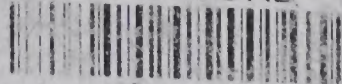


The BODY FUNCTIONS

■
RALPH W. GERARD

THE SCIENCES
A SURVEY COURSE FOR COLLEGES
■
Edited by GERALD WENDT

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Body functions

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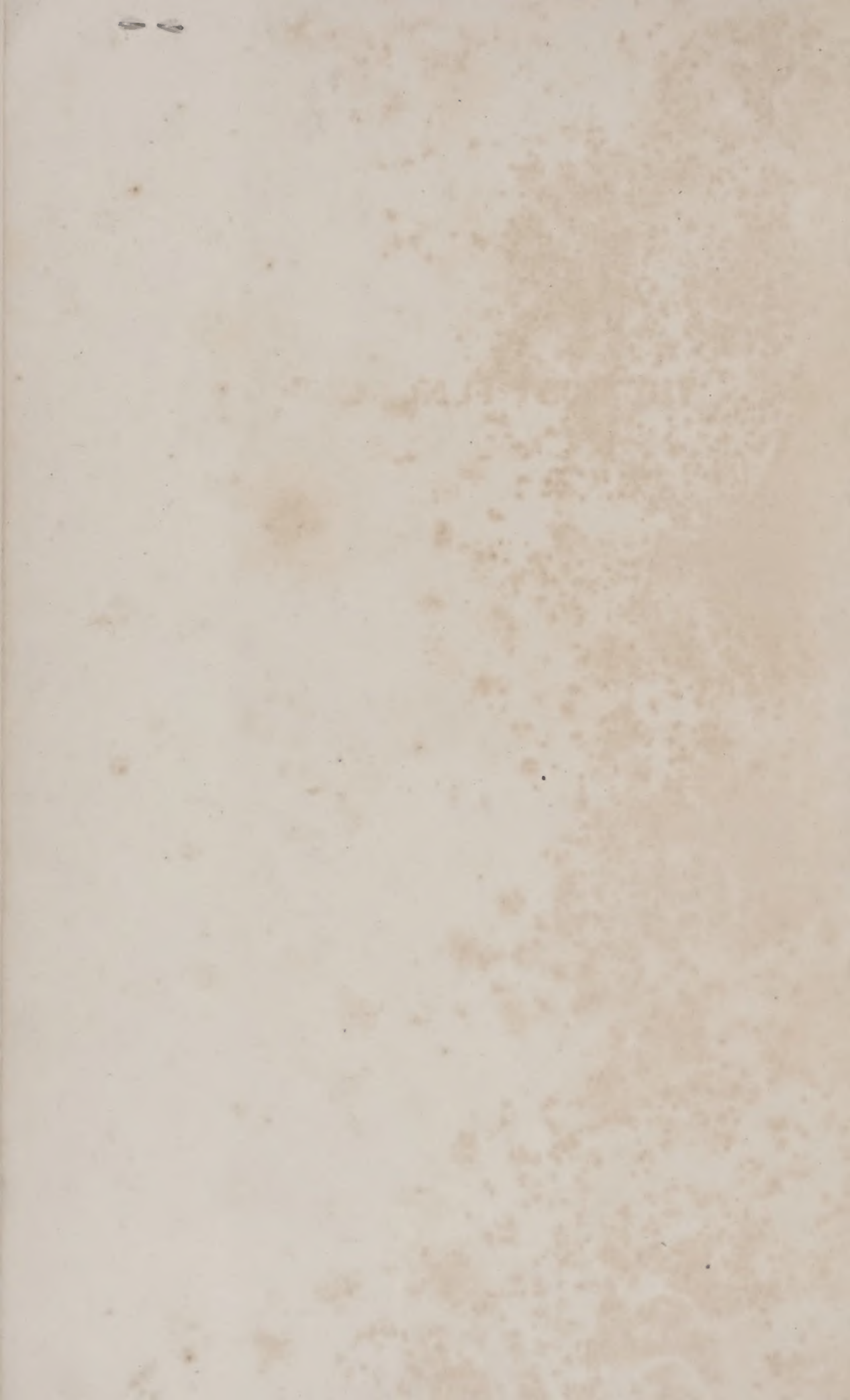
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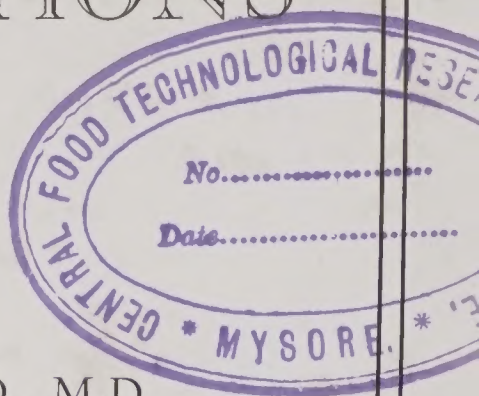
THE BODY FUNCTIONS

Physiology

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THE SCIENCES

A SURVEY COURSE FOR COLLEGES

EDITED BY

GERALD WENDT, PH.D.

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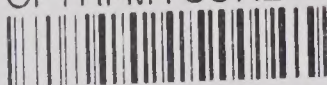
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To my wife
"DR. MARGARET"
who really got this book written

9

THE SCIENCES

EDITOR'S PREFACE TO THE SERIES

Science has many aspects, but above all it is the best use of the human intelligence to improve the conditions under which we live. In order thus to control our environment the first purpose of science must be to study and understand it. This understanding has built civilization, produced our wealth, determined many of our institutions, and has molded even our intimate outlook on life. It has become a powerful social force.

Education, on the other hand, is primarily the adjustment of each individual to his environment, thereby fitting him for a successful place in it and for a happy life. It is the simplest logic, then, to conclude that an understanding of science is an essential element in everyone's education.

Though this truth is not seriously disputed, it is nevertheless seldom that a college curriculum accords with it. The reason lies in that extreme of specialization which alone makes scientific research possible. Courses in science taught by successful specialists have for decades looked primarily toward the professional training of more specialists. This purpose has far outweighed the need of future citizens for a broad understanding of the universe and for learning the best use of the human intelligence. Technical courses in the various sciences have, indeed, long been offered to every student, but they rarely aroused his interest and seldom met his needs.

In recent years numerous efforts have been made to survey science as a whole and to present it as an integral part of a liberal education. It is not difficult to sketch the scene superficially, but the result is a smattering of descriptive knowledge which is far from being science. It is also possible to select important technical phases of each science and to ease their

gravity with a froth of light words. But this too is not enough. The student and the citizen need to absorb the scientific attitude, to master the scientific method of thought, and to understand the basic concepts of the sciences. Only thus, delving beneath the superficial and avoiding the burden of the technical, can they be ready to read further and to understand in the decades to come what science is doing and can do. Only thus can their own intelligence be called into play.

Hence in this series the basis of selection is such understanding. It has been a difficult choice, for each author is keenly aware of great and important topics omitted or scantily treated. Yet condensation is mandatory. Each author in the series is a master of his own subject and each has surveyed his field from this point of view—to present what is most needed for broad understanding, to omit all that is likely to be forgotten in any case, and to prepare the student for life in the second half of the twentieth century.

Each book is an essay in itself, but the books of the series may be combined in any number and in almost any order to form a comprehensive and liberal course in science. Each contains ample suggestions for further reading.

It is apparent that the needs of college students in such a course are no different from those of any intelligent citizen in search of education, or even of college graduates seeking to fill the great gaps left in the curricula of former years. They too have questions that remain unanswered in the light, fantastic books of “popular science” and that are only aggravated by the ponderous technical textbooks. They too need the essential concepts, the method of thought and investigation, and the distinctive intellectual attitude of science.

Thus we hope that this provides the answer—a brief but significant survey of the fundamental sciences, an elementary but sound foundation for the further study, but above all a key to the understanding of our environment and of the possibilities inherent in science.

GERALD WENDT
Editor

PREFACE

This book is about you and me. A very personal document, indeed, it deals with what is under our skins and how it works. When you come right down to it, most of us keep much the same relation to our bodies as we do to our automobiles. As a running machine, we know roughly what goes in and what comes out and the sort of performance that can be expected. We “gas-station” ourselves three times a day, garage up at night, and wash the body at varying intervals. The female variety of human machine has even taken to simonizing. We idle or race our motors and sometimes have to go to the repair shop.

But look under the hood, we do not. Perhaps it is just as well for most of us not to tinker with our human machinery but to leave that to expert mechanics when, rarely, this is necessary. For the human machine differs from the automobile in two seemingly contradictory ways: it is more intricate and depends on a far more perfect balance of many parts and processes; and at the same time it is self-adjusting and self-repairing, so that this elaborate balance is automatically maintained. The expert juggler not merely keeps more balls in the air more of the time, but more promptly and successfully corrects any slight error which would send the lot tumbling down.

But, still it is one thing to avoid tinkering with the machinery and another to know nothing about its workings—we can at least peer under the hood, while studying the instruction book, with no harm; and we may perhaps discover things which will help us to run the body a little more wisely. This automatic balance is the main theme of Part I of this book.

A happy circumstance and one which is no accident is

that living machinery, like non-living, has certain broad characteristics in common. Much of what is true for man is true for his dog and his cow, for the snakes he avoids and the fish he seeks, even for the wheat he grows and the tree that shades him. Perhaps you have already learned some of the universal properties of living things: the essential likeness of their protoplasm; their organization into cells and tissues; the presence in them of water and salts, of sugars, fats, and proteins; their continuous chemical activity, their ability to grow and reproduce, and their response to changes in their surroundings. Now our problem is to go further in one individual case and examine the particular ways in which certain living things have solved the general problems which confront all. This is the emphasis in Part II.

Plants and animals—crocuses, crayfish, crocodiles, crows, and cats—have all found different ways of doing the same things. The ways of mammals in general, while differing from each other in details, are essentially alike as compared to the ways of less-related types. Dissecting a cat or operating on a dog teaches us much about man, for the same organs are present in about the same positions in all three and perform the same duties in the same manner.

The treatment of diphtheria was worked out by experiments on guinea pigs, that of diabetes on dogs; the serums used to prevent lock-jaw and other ills are prepared from horses or sheep; and the gland extracts which prevent a wasting death come from cattle.

An understanding of malaria came from a study of spotted fever in cows, and the prevention of distemper in dogs resulted from studies on smallpox and similar virus diseases in man. Rabies attacks man and his dog alike, and both are indebted to Pasteur for experiments which led to its near eradication. It follows, then, that we may learn from the experimental study of related species much which applies to man with no restrictions. Here we go. If your curiosity leads you to travel still further, the readings indicated at the end of each chapter are signposts for further knowledge.

I cannot close this foreword without a word of thanks to the many who have helped me in preparing this volume. Drs. Victor Johnson, Arno Luckhardt, and Howard Swann have each read the entire manuscript and have helped eliminate errors and given other constructive criticism. Dr. Helen Carlson and Mrs. Maxine Smith helped prepare the manuscript, and the former also ably helped select the illustrations and is responsible for several of the original records and photographs in the illustrations. For the many newly drawn figures I am indebted to the skill of Mrs. Patricia McCuaig and Miss Evelyn Madsen. Particularly I would thank the editor and the assistant editor of this series, Miss Catherine Emig, for continued advice and assistance from conception to press.

RALPH W. GERARD

CHICAGO, ILLINOIS
November, 1940

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THE BODY FUNCTIONS

PART I

CHAPTER I

MUSCLE AND OTHER EFFECTORS

CELLS THAT PRODUCE AN EFFECT

After all is said and done it's what we do that counts. But just what is meant by "do"? Often we distinguish people who do things from those who talk or write about them. Yet writing and talking are certainly mild forms of exercise; writer's cramp and orator's throat result from overworking the small muscles on which these activities depend. Could we then say that "doing" is moving some muscle? This would, indeed, cover a great deal, more perhaps than we expected; for the beat of the heart and the movements of the stomach and intestine are also muscle contractions, though of somewhat different kinds of muscle. Yet our conception is still too limited. As I write this on a hot July evening I am uncomfortably aware of doing something else—perspiring freely. And think of the times our mouths water or our eyes; are these not, also, things we do? Perhaps we shall not be far wrong if we include all kinds of muscle contractions and gland secretions as "the things we do." Such cells, the ones which produce effects, we can group together and call effectors.

Muscle and gland are the effectors of man, but many more exist in various animals—those which produce the flash of the firefly and the shock of the electric eel, which change the color of the chameleon, which enable the jellyfish to sting, and a host of others. In each case the effector is a cell, or usually a group of cells, which has developed some special form and

special capacity for doing just one job particularly well. These are the final performers for the body and must, of course, be



FIG. 1. Skeletal muscles are attached at their ends to different bones which can move relative to one another. The attachment which is relatively fixed—in this figure, that to the thigh bone above—is called the “origin”; the attachment, usually through a narrow tendon, which is more movable—in this figure, that to the shin bone below—is the “insertion.” Here are shown two muscles which respectively extend and flex the leg at the knee. The “extensor” muscle contains the knee cap in its tendon; the “flexor” muscle has the more usual simple tendon. (Drawn by P. McC.)

controlled by it. In one sense, everything that happens within the organism is directed only to enabling these cells to perform.

STRIATED MUSCLE

In man, acts are overwhelmingly muscle movements. Still more, they are movements of a particular kind of muscle, plastered all over the surface of the body just below the skin

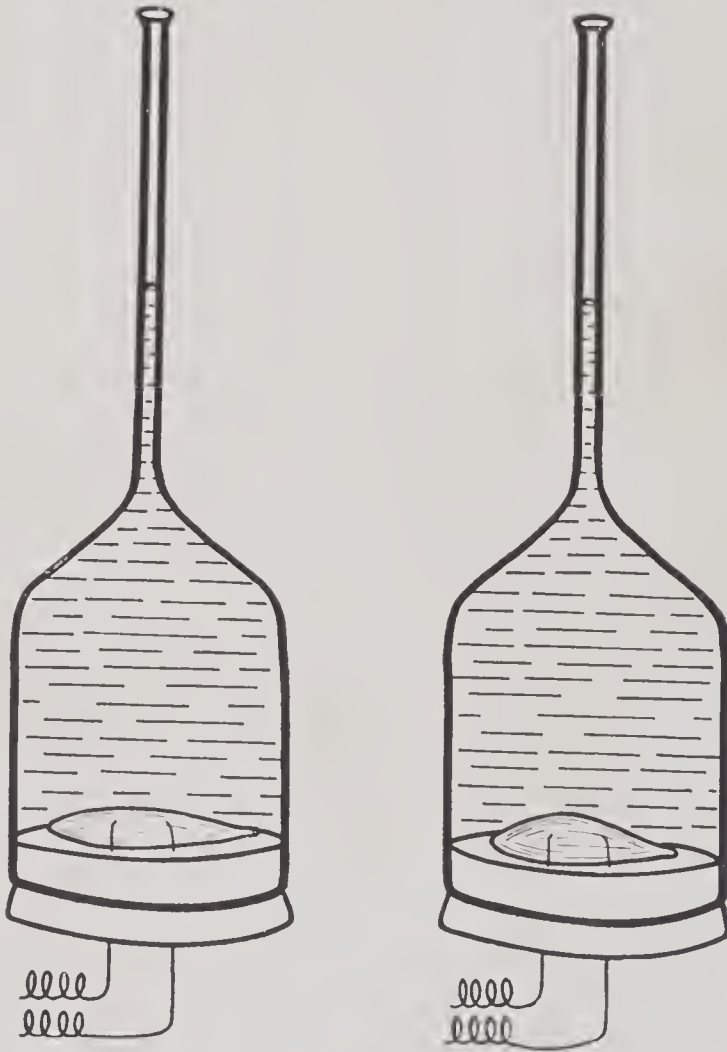


FIG. 2. This is roughly the apparatus used in the first experiments which proved that a muscle does not decrease its volume when it "contracts." The level of fluid in the capillary tube above does not change when the muscle is made to shorten by electrical stimuli delivered through the wires. Actually, with far more sensitive instruments, it has been possible in recent years to demonstrate minute volume changes; but even these may be in the direction of increase as well as decrease, depending on conditions. (Drawn by P. McC.)

and attached to most of the skeleton; hence called skeletal muscle. It is hardly surprising, then, that skeletal muscle, also called striated muscle from its appearance under a microscope, makes up over half our weight. So let us study first the all-important action of striated muscle.

CONTRACTION. We say muscle contracts, that is, draws together or shortens. This is right enough, though the word originally implied that the active muscle had shrunk and was smaller than while at rest. That this is not so was shown only two centuries ago by the Dutch scientist, Schwammerdam, in an experiment you can easily do yourself. The fat spindle-

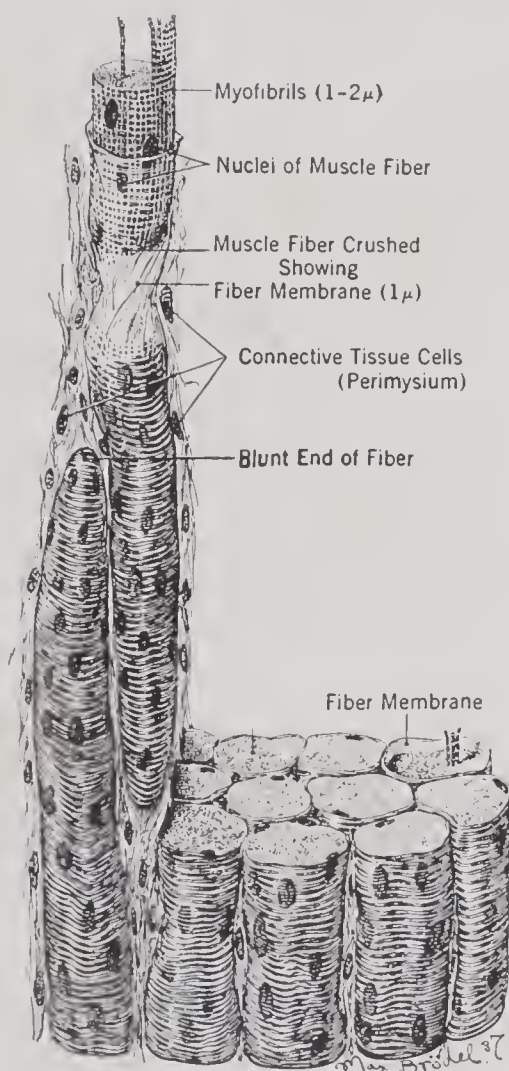


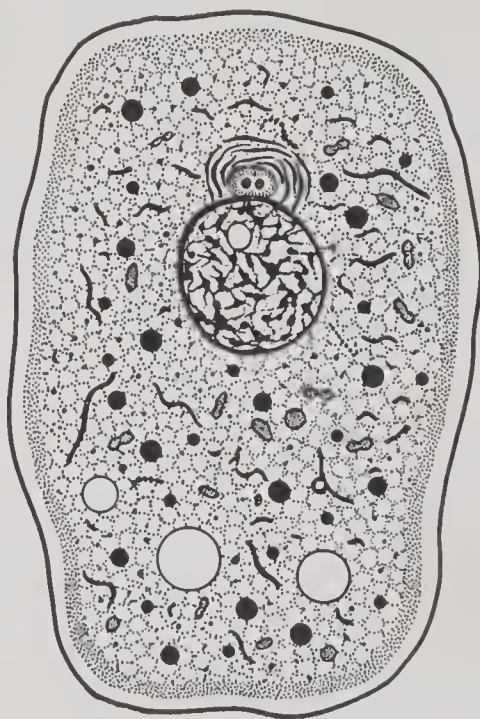
FIG. 3a. Here is shown a small group of striated muscle fibers, illustrating the manner in which they are arranged so that all lie in one direction. Most of the fibers are cut off in the picture, but one is left to give some idea of its length and shape. The regular transverse striations so characteristic of this type of muscle are indicated, and you can also see the many dark oval nuclei scattered along the fiber under its membrane. It would not be proper to speak of the muscle fiber as a muscle cell for it is a sort of super-cell or syncytium formed by the joining together of many smaller cell elements—hence the many nuclei of each fiber. The muscle fiber is, therefore, a highly specialized structure which you may be interested to compare with the more typical cell shown on the next page. (Courtesy Max Brödel, from *Lesions of the Rectus Muscle, etc.*, by Cullen-Brödel, Bulletin of Johns Hopkins Hospital, Nov. 1937.)

shaped muscle which forms the bulge of the calf was taken from a frog's leg and dropped into a liquid. Two wires, by means of which the muscle could be given an electrical stimulus, were introduced and the glass container drawn out at the top into a fine long tube into which the liquid rose. When the muscle was then made to contract, the liquid level remained unchanged, proving that the volume of the muscle was also

essentially unaltered. Indeed, knowing as we now do that the muscle is over 70 per cent water and the rest solids of various kinds, all of which are quite incompressible under ordinary forces, we could hardly expect any other result.

Organization for shortening. The contracting muscle, then, does not appreciably change its volume but does change its shape. This is a bit peculiar when you think about it. Of

FIG. 3*b*. The "typical" cell, not especially differentiated, is composed of a mass of cytoplasm surrounded by a cell membrane and containing a major cell organ, or organelle, the roughly spherical nucleus somewhere near the center. The cytoplasm contains other structures, such as granules of specific composition, fine threads, loosely interwoven strands and films, and even special canal systems; but these need not worry us especially. The cytoplasmic fluid in which these microscopically visible structures are suspended, furthermore, is itself composed of ultra-microscopic colloidal particles floating about in the protoplasmic water. The microscopic particles, as well as the ultra-microscopic ones, are arranged without special pattern or orientation in this cell; but in the specialized muscle fiber most of them are located in set regularly repeated positions, to form the characteristic striations and to serve the specialized function of shortening. (From Gerard's *Unresting Cells*, by permission of the publishers, Harper and Brothers.)



course muscles are not symmetrical to begin with. One dimension is greater than the others, and it is at the two ends of this "length" that the muscle is attached to bones; but just because it is elongated is no reason that this greater dimension should become less and the other two greater when the muscle is excited—a strand of taffy would show no such trick. Obviously the muscle along this one axis must be different from what it is along the others. That muscle does have a sort of grain is obvious enough when we cut meat, and the basis of it be-

comes perfectly clear under the microscope. For the bulk of the muscle is built of thousands of long slender cylinders, the muscle fibers, lying parallel to each other like well-packed straws.

A single fiber, though perhaps only a fifteenth or a twentieth of a millimeter in diameter, may run for a centimeter or more, the whole length of a short muscle. The fiber has many nuclei and is really not a single cell but several dozens of them which have pooled their cytoplasm and their interests in a type of communal supercell (syncytium). Parenthetically, is it not remarkable that these fibers, and indeed the main muscle axis, should be oriented so neatly to exert just the most effective pull upon a bone, however they may be placed in relation to the whole body? Is it not possible that the pull itself somehow controls the direction they come to take? It seems so, for when a muscle is released from all pull by having its tendon cut away the fibers lose their direction and degenerate.

To return to contraction, we can still ask the same question about the single fiber that we asked about the whole muscle: why should it become shorter and fatter when it is active? This also must have some structural asymmetry, some longitudinally oriented components. The microscope again shows this to be true, for very fine fibrils run along the fiber like strands in a rope. We ask our question still again, and the microscope can no longer answer it. But scientists have a way of inventing methods to find out what they wish to know. By studying muscles with polarized light, beams of X-rays, and other special agents, it has been possible to show that the submicroscopic particles, of which the fibrils and even the fluid between them are built, are elongated rodlets or micelles; and, even more, that these micelles are constructed of sheaves of thread-like protein molecules. So, from the large elongated muscle to the minute elongated protein molecule, the entire edifice is built of parallel, stretched-out architectural blocks. If the protein molecules were somehow made to wrinkle up on themselves, the muscle would contract.

The machinery of contraction. A protein molecule is built of a very long chain of carbon and nitrogen atoms, two carbons

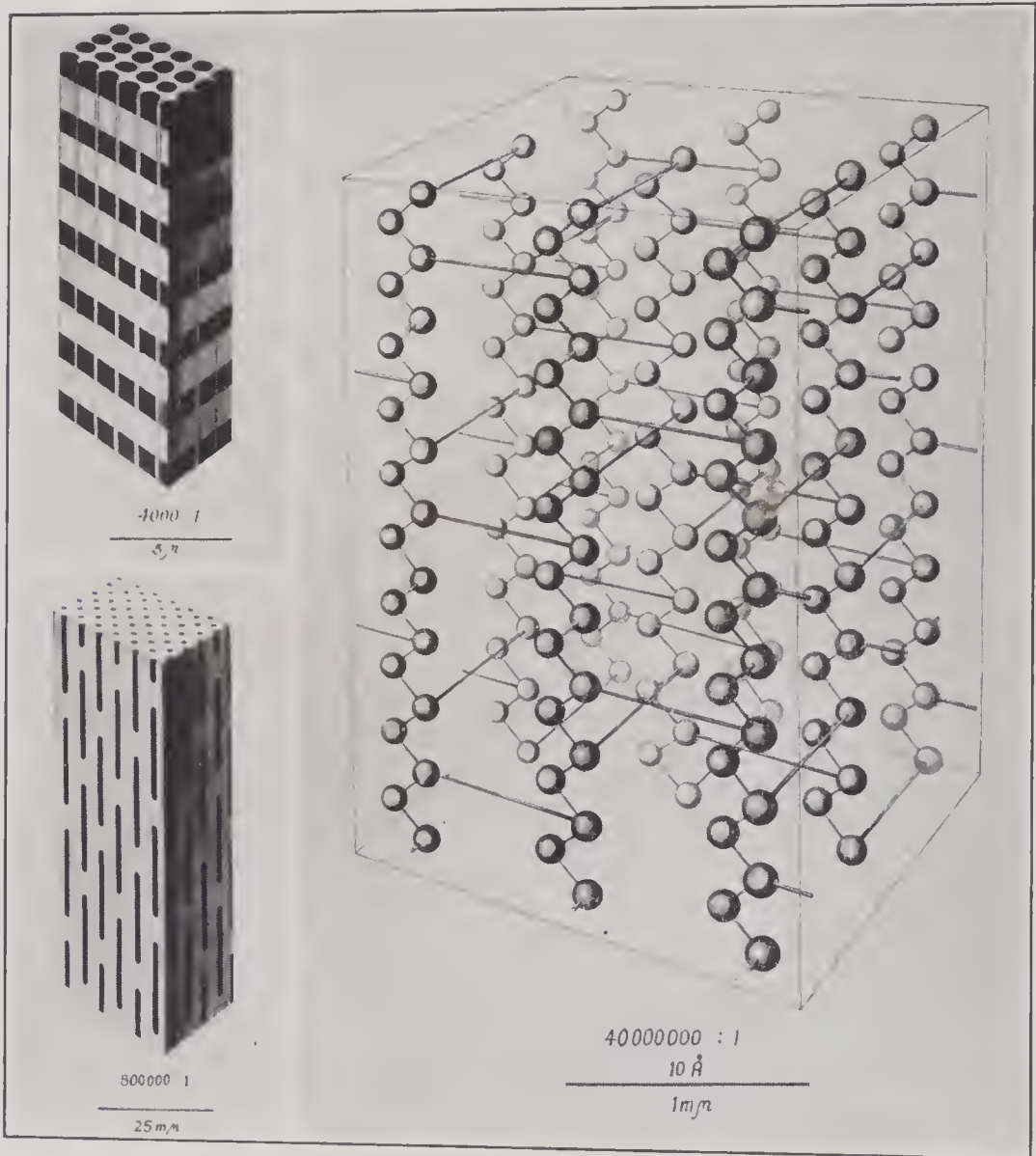


FIG. 4. Diagrams of the structure of a muscle fiber at three progressively greater magnifications as indicated. The upper-left diagram shows a group of striated muscle fibrils in a single muscle fiber; and the lower left shows the micelles arranged longitudinally in a single fibril. On the right is a model showing the "backbones" of several elongated protein molecules in a micelle, with side connections between different molecules indicated by the horizontal bars. (Courtesy of Dr. Ernst Fisher.)

alternating with one nitrogen, and with a larger or smaller group of atoms attached to the first carbon in each triplet. The whole is not unlike a grape vine with tendrils and leaves

sprouting out at fairly regular intervals.* These side groups of atoms, however, are often most unlike one another. Some are weak acids, others bases; some are able to act as both, others as neither; and in nearly all cases, the acidity, salt content, and

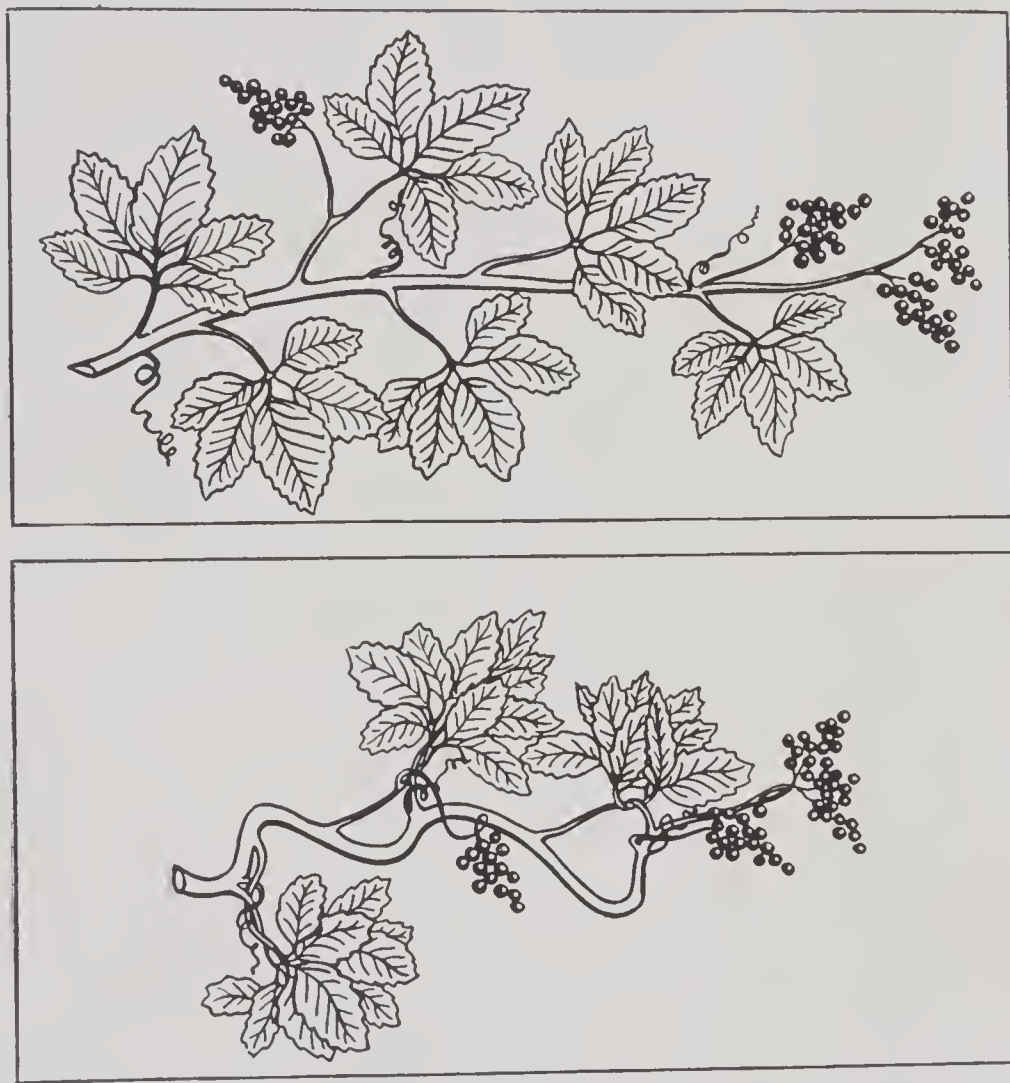


FIG. 5. The "stem" of a protein molecule buckles and shortens when its side groups combine—as if leaves and tendrils of a grapevine became tangled together. (Drawn by E. M.)

other characteristics of the solution in which they find themselves determine whether they are free of one another or combined together. When acid and basic side groups near each other are both available, they are attracted together and may

* In case you are not comfortably familiar with the chemical notions used here, the diagram of the protein molecule and discussion in Appendix A may be of service.

form a temporary combination. The effect is to buckle the backbone of the molecule and, if many such combinations occur, the protein chain becomes considerably folded and shortened. Here, then, is just the machinery needed for contraction. A small change in the acidity of the muscle protoplasm—and actual measurements show that the muscle becomes more

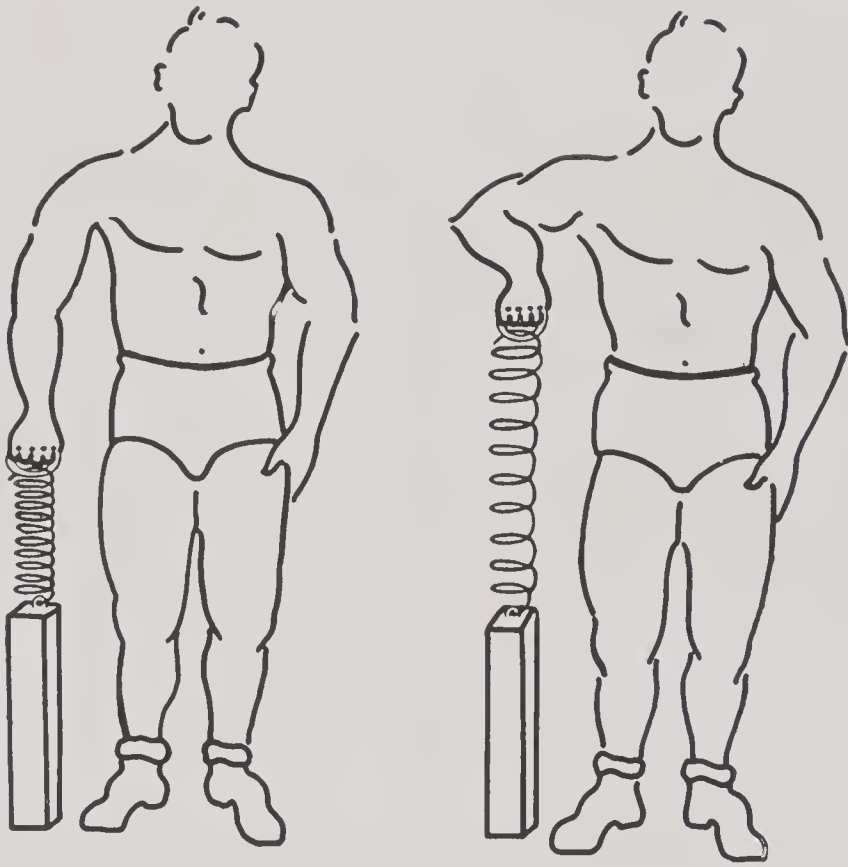


FIG. 6. If the protein molecules in the muscle micelles acted like coiled springs then, as shown here, the real work must be done in stretching them out. When they shorten again, as during contraction, they can release this stored energy and do work. The real job for the muscle, then, is to again relax and stretch its proteins. (Drawn by P. McC.)

alkaline just at the beginning of contraction—will suffice to curl the protein molecules, to shorten the muscle, to move a leg, and to start us going places.

Energy for contraction. Of course we must investigate the chemical changes which lead to this alkalinity, but another question is more urgent. In response to a single stimulus (and how this acts must also come later) the muscle contracts and at once relaxes again. It gives a single twitch, which may last

far less than 0.1 second, yet develops within this time enough tension to lift a weight fully 500 times as heavy as itself. Now we might say that, if adding a little alkali makes the protein molecules curl up, then taking it away or adding the equivalent amount of acid would make them stretch out again. But this

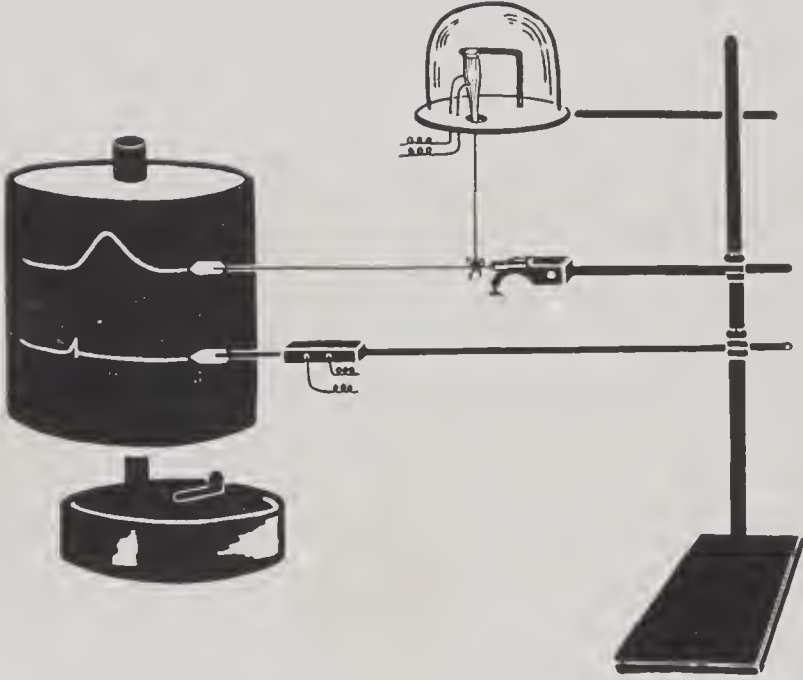


FIG. 7a. The frog's gastrocnemius muscle is placed in a "moist chamber" which prevents its drying out and one end is attached to a rigid bar, the other by a thread to a lever which is lifted as the muscle contracts. The electric stimulus is delivered to the muscle through wires; and in the same circuit is included the "signal magnet," shown below the muscle lever, to indicate the instant at which the stimulus is delivered. The muscle lever and the indicator of the signal magnet carry at their tips light paper or celluloid writing points, arranged to touch the surface of the moving cylinder in the same vertical line. At the left is shown a "kymograph," the large drum of which is turned at a constant desired speed by a clockwork mechanism in the base. Wrapped around the drum is a sheet of glazed paper which has been blackened by turning it in a sooty flame. The writing points, by scraping off the soot, trace a white line upon the moving drum. The record of a single muscle twitch is shown. (Drawn by P. McC.)

is too easy, for somehow a tremendous force has been released to do work; and living machinery, as other kinds, must pay the full cost of energy for work. If we think of the stretched protein molecule as an extended spring, then releasing the catch (adding the alkali) allows it to coil up by virtue of its own potential energy of strain. The side groups may have needed just this little chemical aid to succumb to a great atomic yearn-

ing for each other. But if this is so, and it seems to be, then the restretching of the spring or molecule demands that as much fresh energy be put into it as it previously delivered on shortening. In other words, though we have explained contraction partly, this mechanism by no means automatically accounts for relaxation.

Relaxation and contracture. In fact, though contraction is the essential action for the animal possessing the muscle,

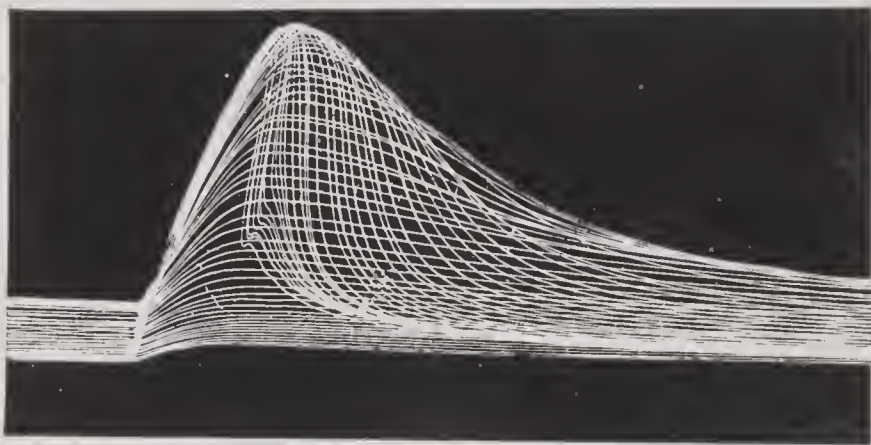


FIG. 7*b*. The apparatus shown in the first half of this figure serves nicely to study the effect of fatigue on the shape of a muscle twitch. The drum must be kept turning rapidly and an arrangement made so that the muscle is stimulated once on each drum revolution at just the same point. The successive twitches thus show as more or less superimposed traces. This record, of such an experiment, shows the progressive decrease in height of contraction associated with the very striking prolongation of relaxation. The twitches of the rested muscle at the start are thus high and narrow, those of the fatigued muscle at the end are low and very prolonged. The extra notch, on the falling part of the curves which drop most rapidly, is an effect of the apparatus. Note that the first few twitches increase in height as well as duration (the "staircase phenomenon") before they get lower and longer. (Courtesy Dr. Erma Smith.)

relaxation is the important thing for the muscle itself. It is a greater problem to make a stick of dynamite than it is to explode one; and the contraction which "explodes" the muscle must be followed by the manufacture of another charge in readiness for the next time. Once this is clear, many things, which would otherwise seem odd, follow automatically. When our muscles are fatigued they sometimes go into cramps; when the frog's gastrocnemius (calf muscle), or any other muscle, is made to give a twitch every second or so, for hundreds of times, its increasing fatigue can be seen in the altered shape of

the contraction. The striking change is not in a progressive failure to contract but in an ever-slower and more laborious relaxation until, when the fully fatigued muscle can respond no more, it has lost the power to relax and so remains permanently shortened.

Such maintained shortening, called contracture rather than contraction, can be brought about in many ways and is a more common consequence of killing a muscle than is the relaxed state. Rigor mortis, for example, so popular in detective fiction, is a contracture. We shall see that sugar, on being burned or fermented, supplies much of the energy for a muscle twitch and that a moderate reserve of this is stored in the muscle. Can you figure out now why rigor mortis is likely to appear sooner in a half-starved person who had been taking violent exercise than in a fat, well-fed one shot through the back of his lounge chair?

Moving and bracing. However anxious we are to get on with the interesting chemical changes in muscle, there are a number of important things about the actual contraction still worth our attention. For example, we probably contract our muscles far more often without their really shortening at all than we do with shortening. All the time that you are standing or holding your head up or even keeping your jaw from sagging open, the pull of gravity is being resisted by a steady unmoving contraction of the appropriate muscles. When the extensor muscles, which straighten the leg at its various joints, are paralyzed, the leg gives under the slightest weight. You know this from what happened when you tried to stand on a leg that had "gone to sleep," that is, became temporarily paralyzed, by keeping it compressed. Further, when you hold the end of a piano up while waiting for someone to slip a castor in place, your muscles are contracting for all they're worth—but are not shortening.

Again we can take an isolated muscle to study more exactly how this works. When one end is firmly fixed to a rigid support and the other attached to a light movable lever, the actual shortening during the twitch is easily measured. Our

now familiar frog's muscle, about three centimeters long, will shorten approximately one-quarter of its length. No force resists it, so while its length changes the tension it exerts remains constant. This sort of contraction is called isotonic, or of constant force. Of course the work done (the weight lifted multiplied by the height to which it is lifted) is zero in this case, for the muscle gave a good lift to nothing. If we now add progressively heavier weights, the height to which each is lifted becomes less and less until the weight is so heavy that it is not lifted at all.*

But although the heavy weight is not lifted, the muscle has not been inactive—see how quickly your arm tires of

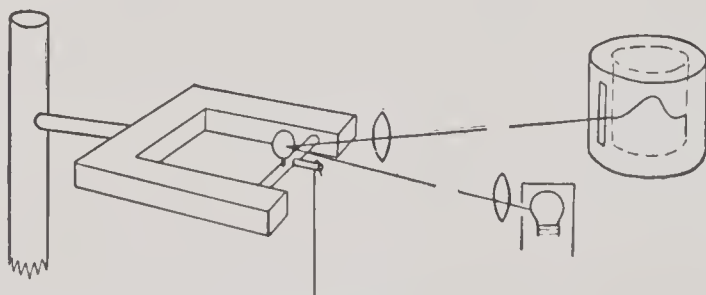


FIG. 8. Arrangement for recording an isometric contraction of a muscle, which would be attached to the wire running to the bottom of the picture. (From Gerard's *Unresting Cells*, by permission of the publishers, Harper and Brothers.)

holding a full milk bottle at arm's length—it has given a contraction at constant length, an isometric contraction. To study this, we can no longer depend on the change in shape but must directly measure the tension developed. This is a little harder but not really difficult. Instead of pulling on a weight, the muscle is attached by a stubby arm to a stiff steel bar which twists ever so little under the muscle's pull. A mirror fastened to the bar twists with it, and a beam of light reflected a long distance onto some photographic paper moves a great deal as the bar twists a little, like the shaft of light from a rotating airplane beacon.

* Will a muscle twitch do most work when it lifts no weight, when it works on a weight that it cannot lift, or when it lifts some intermediate weight some intermediate distance? Can you devise and perhaps carry out an experiment to find out just how great a weight in grams should be used to get the maximal work from a frog's muscle; or from one of your own?

Tension and shortening. Now let us give the muscle, mounted in this instrument, a single stimulus and see how its twitch, measured as a tension, compares with the twitch we earlier measured as a shortening (Fig. 9). The two curves both rise from and fall back to zero and can, of course, be adjusted so that the maximum heights reached in between are equal; but there the similarity ends. Whereas shortening did not even start for 0.01 second and required nearly a twentieth of a second to reach its height, and relaxation had not finished until a tenth of a second after the muscle was

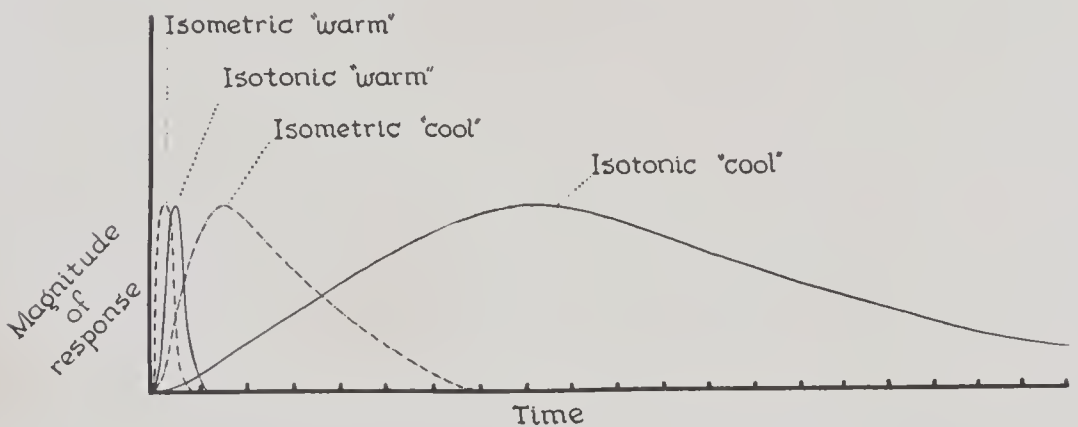


FIG. 9. The time course of a single muscle twitch at room temperature (20°C.) and when the muscle is cold (0°C.). At each temperature is shown an isometric contraction (broken line) giving the rise and fall of tension, and an isotonic contraction (continuous line) giving the actual shortening and relaxation. Note that cold slows the shortening much more than it does the development of tension. (Drawn by E. M.)

excited, the tension begins to mount in 0.003 second, reaches its peak in a hundredth, and is all over by 0.02 second, when shortening has just got well under way. This is a serious discrepancy between the force exerted and the movement it produces and could not possibly be caused by ordinary inertia, or resistance to change in movement, for the time and mass involved are impossibly out of proportion.

Well, then, could the delay be due to a kind of friction, an internal friction in this case, caused by the movement of the colloidal* micelles past one another; due, that is, to the viscosity of the muscle substance? It is just such internal

* A word about colloids may help you. See Appendix B.

rubbing of its units past each other which makes oil flow more slowly than water, and molasses more slowly still. It is possible to measure the viscosity of a muscle by suddenly giving it a passive stretch (pulling it by an external force, the reverse of making it actively contract) and noting the speed and ease with which it yields to the pull. As you might expect of such a semi-solid, its viscosity is indeed high, quite enough to account for the lag between tension and shortening. Further, viscosity is greatly increased by cooling, so that, if this is actually the reason for the lag between tension and shortening, this lag should be much exaggerated when a well-chilled muscle is made to contract. It is.

To return to our picture of a stretched spring suddenly released, we have now but to add that it is surrounded by glycerin or molasses to make it fit our additional understanding of the muscle. If the spring is connected to a tension measurer which does not allow movement, the spring's full tension will be expressed as soon as the catch is released, for the viscous fluid makes no difference until movement has occurred. But if the movement rather than the tension of the spring is measured, this will be greatly slowed in the glycerin and lag far behind the shortening in air.

Gradation of contractions. There are, however, further tricks about a muscle contraction which are not so easy to parallel in our spring model. For example, how could one spring, when released, do anything but coil up to its resting length, however slowly it moved? But the amount of shortening of a muscle in response to a stimulus can be very variable. It would be awkward if this were not so, for every time one attempted to scratch his nose, he would deliver a knock-out punch. A weak stimulus to the muscle gives a feeble contraction, a stronger stimulus a more powerful one. Perhaps you are thinking this is no problem at all, for each of the several thousand muscle fibers is able to contract as a unit and independently of the others; and it is obvious that a weak stimulus could cause only a few to contract, a strong stimulus, many. Very well, if your explanation is correct, what should

happen to the height of the twitch when you test the muscle with stronger and stronger stimuli? The results of such an experiment are shown in Fig. 10; do they bear out your predictions?

Summation of contractions. Let's start again and stimulate the muscle so powerfully that we are certain every fiber is participating. A maximal twitch results. Now what will hap-

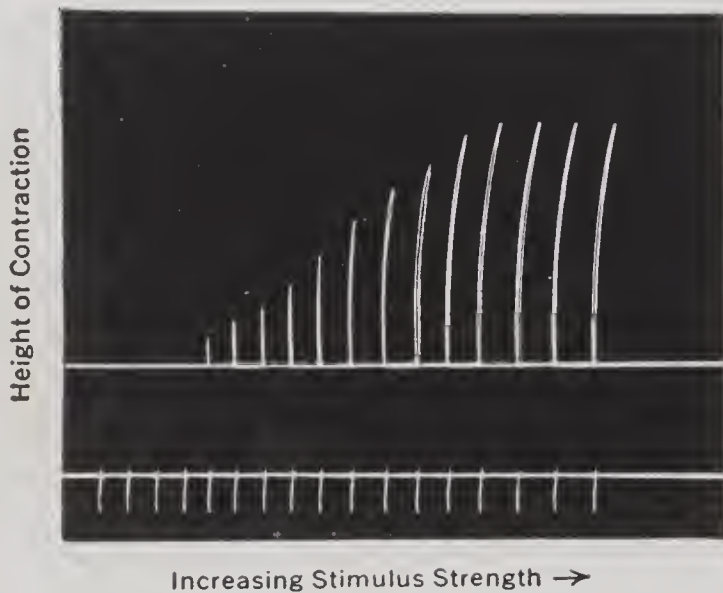


FIG. 10. This record shows the variation in strength of contraction of the muscle with variation in the strength of the stimulus given. The lower line shows the marks of a signal magnet, each down stroke indicating that a single shock was given to the muscle at that moment. The upper record shows the movement of the muscle lever, and the length of each vertical line thus measures the height or strength of the resultant contraction. Successive shocks, reading from left to right, were made progressively stronger by approximately equal increments. You will note that the weakest stimuli are subthreshold and bring about no response. As the stimuli increase in strength a muscle contraction appears and increases up to a "maximal" contraction. Further increase in strength beyond a maximal stimulus does not produce any further increase in the contraction.

pen if a second stimulus is given while the muscle is still shortening in response to the first one? We can make several guesses, but without, as yet, having much confidence in any one. The second stimulus might, for example, find the muscle already fully occupied and so non-responsive to it, or refractory. We shall see later that this does occur in most cases when the two stimuli are close enough, separated by not more than 0.002 to 0.003 second. Or the second stimulus might simply keep

the muscle contracted for a longer time. This we shall examine shortly. We should hardly anticipate, however, that the twitch in response to two stimuli, each one “maximal,” would be larger than that to one. Yet this is exactly what happens. There is, we say, a summation of contractions, so that the total shortening (or isometric tension) is greater than that of a single twitch. Actually, not only two but several closely timed successive stimuli cause ever-higher contractions. A tetanus, the name for the muscle response to such a regular train of



FIG. 11. As repeated maximal stimuli (indicated by the signal magnet tracing below) are delivered to a muscle at shorter intervals, the muscle twitches follow ever closer on each other's heels so that relaxation is more and more interfered with. When the stimulation frequency is high enough, some fifty a second, the single twitches become completely fused into a smooth tetanus which is maintained during the entire period of stimulation. Note that in such a tetanus, seen on the right, the muscle is more contracted than during a “maximal” single twitch.

stimuli, may be two or three times as great as a single twitch; and, barring fatigue, this height will be maintained as long as the stimuli continue.

Stimulation and response. Do you see that this behavior presents two important problems? First, how can the muscle shorten more, or produce more tension, than its “maximal” response with all fibers participating? Second, how can this tension and shortening be maintained for long times without the usual relaxation at the end of each separate twitch? (Have you already thought that most—actually all—of our movements last far longer than 0.1 second and must, there-

fore, be tetani rather than twitches? This is even more true for the postures we maintain for minutes or hours. How jittery we would be, with our muscles twitching on and off, if this were not true!)

The stretched spring, we saw, would contract fully or not at all; and a large number of small springs lying side by side, separately releasable, would parallel the throwing into action of varying numbers of muscle fibers. But this model would not help us understand the varying twitch of the single fiber. For this we would need a somewhat improbable, though not impossible, arrangement of a series of catches along the spring, each of which could be released only after the preceding ones. But this introduces new dissimilarities from muscle, and perhaps the time has come to leave this obviously imperfect model and look again at muscle itself.

There is nothing about the coiling of a protein chain in the presence of alkali that should make it behave in a critical fashion—that is, like the sudden release of a spring or the firing of a bullet by a trigger. In these cases, when some minimal or threshold amount of change has been imposed upon the system, the spring or powder is set off and then carries on under its own energy. The response it gives is, therefore, all of which it is capable, if the stimulus is successful; or none at all, if it is not. This type of all-or-none behavior is extremely common and important in the activity of living things, as we shall see; but the muscle proteins would be expected to shorten continuously rather than discontinuously, more and more as the alkali or other chemical change acting upon them itself increases. This is really the more familiar situation—a rubber band (or a muscle) stretches gradually as the pull on it is increased, water gets steadily hotter as more heat is added, and the color of some dyes changes over much of the spectrum as the solution in which they are dissolved is made progressively more acid or more alkaline. (For example, your tea becomes a paler brown as acid lemon juice is added.)

Actually, it has been shown in various ways that the muscle proteins can, indeed, shorten increasingly with increasing

chemical change in the solution about them. Then why should there be a constant maximal response (when all the fibers are acting, of course) no matter how the strength of a single stimulus is varied? The stimulus itself must somehow act in a trigger fashion to set up a change which does follow the all-or-none relation and which produces, therefore, a fixed amount of alkali following each stimulus. This also has been proved to be true and to depend upon the conditions for spread of excitation down the length of each muscle fiber. But this is essentially the problem presented by nerves, which likewise transmit excitation over long distances, and we had best leave it for examination later on.

So far as contraction is concerned, then, we can think of each stimulus, whatever its strength, as squirting a determined constant amount of alkali upon the protein molecules and, therefore, leading to a fixed amount of shortening. But this shortening is far less than that of which the molecules are capable, so that additional squirts, coming rapidly enough so that the first has not been dissipated by the time the second arrives, can increase the shortening.

This answers the first question which bothered us, and really the second one as well; for if rapidly repeated stimuli continue to deliver increments of alkali as fast as or faster than recovery processes in the muscle fibers can neutralize or remove them, the proteins will simply remain short. An equilibrium is attained between the production of alkali in successive bursts and its steady removal, and the muscle length at any moment will depend on the state of this balance. When, in fatigue or rigor, the recovery reactions are decreased or abolished the muscle remains short although little or no additional alkali is liberated by repeated excitation. Normally, the strength, duration, and even gradation of muscle contractions are regulated entirely by the stimuli delivered to the muscle fibers by the nerves which run to them. You can, perhaps, even now make a pretty accurate picture of how these work, but you will have to wait to check your guesses.

METABOLISM. We have taken it for granted so far that a change towards greater alkalinity in the muscle fiber supplies the immediate condition for contraction, and that its removal, or the production of an equal amount of acid, leads to relaxation. There is a reasonable probability that this is correct, but even if it proved to be wrong this would hardly disturb our general picture. All sorts of other specific chemical changes might supply the necessary conditions for wrinkling the protein micelles. In fact, an increase in acid can itself cause shortening; and since a muscle does become acid under many conditions, it was believed for years that acidity was the means of bringing about shortening. It is hardly more than a decade since new experiments proved, first, that acid production was not necessary for contraction and, second, that the earliest change, even in a normal twitch, is in the direction of alkalinity.

Chemical energy or chemical machinery. The important point for us now is carefully to distinguish two different and often independent functions of the many and complex chemical changes which attend activity of muscle. Certain of them, perhaps very few, are part of the actual cell machinery of contraction, whereas most (and any one reaction may belong in both groups) are necessary only as a source of energy, as fuel with which to drive the machine. Such energy reactions are not individually important and are, therefore, more or less interchangeable. Thus, if alkali does in fact shorten the protein molecules, then it is part of the cell machinery, and the chemical reaction producing it, whether or not it liberates energy, is indispensable; whereas the burning of fat might do as well as the burning of sugar to supply the total energy needed. In the same way, certain particular chemical reactions must occur in a battery for it to develop its voltage; but we can boil water with the heat obtained by burning gas or kerosene or wood or even with the energy of an electric current.

Because these two functions were long confused, the steadily increasing factual knowledge about muscle metabolism required several revolutions in interpretation. Perhaps it will

interest you to learn how some of the greatest biochemists and physiologists of the last fifty years made important discoveries and yet were led to incorrect conclusions about them.

Oxidation. Half a century ago about all that was known of the chemistry of muscle contraction was that a fatigued muscle became more acid than a fresh one and that, if it were then allowed to rest with an adequate supply of oxygen, the acid and the fatigue both disappeared. Even after a few twitches, it was found that the active muscle used oxygen at a greater rate than did a resting one during the following half hour or more; and if this extra oxygen consumption were prevented, by keeping the muscle in nitrogen, the number of twitches subsequently obtainable was greatly diminished. In other words, without oxygen the muscle failed to recover between contractions and so ran down. You know this well enough from indirect evidence; after going all out in a hundred-yard dash in ten seconds (if you're good enough) you continue to gasp for many minutes and your heart takes even longer to slow down to its usual rhythm. The more rapid breathing and blood circulation are necessary to supply the muscles with the large amount of extra oxygen they need during recovery.

Fermentation. The first striking advance in knowledge was made by two English scientists who proved that the acid in question was lactic acid, the substance bacteria make from sugar when they sour milk; hence its name, milk acid. Now the chemical formula for glucose, the ubiquitous grape sugar found in practically all cells and body fluids, is $C_6H_{12}O_6$; and that of animal starch or glycogen, which is stored especially in the liver and muscles, is essentially the same except that many, perhaps hundreds, of the glucose molecules have become combined into a single large molecule. The formula for lactic acid is $C_3H_6O_3$, so that one molecule of glucose might obviously form two of lactic acid; and one of glycogen, a proportionately greater number. Note that there is no question of oxidation when glucose or glycogen changes in this way, for the sugar is split into equal fragments with no addition of oxygen or loss of hydrogen atoms.

Actually we know now that this apparently simple change is an extremely complicated one and that some two dozen other substances, including phosphate compounds, are formed by as many different enzymes in the cell before arriving at the lactic acid. Under various conditions, one or another of these intermediates becomes the end of the chain and so accumulates and can be measured. Also, under normal conditions, various types of cells carry these same complex reactions to different terminations. Yeast, for example, breaks down sugar in the absence of oxygen—that is, ferments it—much as does muscle; but the process is carried just a little further so that, instead of stopping at lactic acid this is itself broken down to carbon dioxide (CO_2) and alcohol ($\text{C}_2\text{H}_6\text{O}$) (which add up to $\text{C}_3\text{H}_6\text{O}_3$ —lactic acid). The formation of lactic acid, or of alcohol, is a matter of fermentation, also called glycolysis; but its further breakdown into carbon dioxide and water requires oxygen and is a true oxidation. (The chemist would write the reaction as $\text{C}_3\text{H}_6\text{O}_3 + 3\text{O}_2 = 3\text{CO}_2 + 3\text{H}_2\text{O}$.)

Sugar synthesis. By comparing a large number of muscles which had been tetanized with their fellows in the opposite legs which had been left resting, these investigators further showed that just the right amount of glycogen had disappeared in the active ones to account for the newly formed lactic acid. Very well, they concluded, the essential change during contraction is the fermentation of sugar to lactic acid. Then it followed that during recovery, with its extra oxygen consumption, the lactic acid is burned. But here was the first hitch for, though the lactic acid did slowly disappear during the recovery period, all the extra oxygen used then could not suffice to burn more than a fifth of the acid. More analyses were made, and it turned out that, of the lactic acid disappearing during recovery in oxygen, one-fifth was burned, right enough, but the other four-fifths were neatly changed back into sugar. Well, then, why does not this reversion occur when a muscle is kept in nitrogen after contracting, instead of in oxygen?

Heat and energy. This problem is again one of energy. Humpty-dumpty might fall down but would never fall up

again without work being done to lift him. When sugar changes to lactic acid it liberates energy, which can be measured as heat; a fermenting solution actually may get quite warm. To change lactic acid back to sugar, then, energy must be added. When sugar or lactic acid burns, however, a large amount of energy is liberated. (Wood is chemically very similar to glycogen, so you can judge how much heat is given off from such burning!) Oxidation of one-fifth of the lactic acid formed, therefore, releases enough energy to enable the other four-fifths to be rebuilt into sugar and still leave some energy over.

All this can be studied directly by measuring the heat produced by a muscle during and after contraction. If we call that amount liberated at the start, when lactic acid is formed, one unit, then there are 1.5 additional units liberated during the long recovery period. If, however, no oxygen is available, the initial heat appears unchanged—that is, the heat remains in constant proportion to the amount of tension produced, though both decrease together as fatigue advances; but the recovery heat is promptly abolished.

Contraction without fermentation. Everything now seemed to be in order: the lactic acid was needed to produce the actual shortening of the muscle fibers and so was promptly produced in large amounts from sugar; after it had done its work most of it was saved, as sugar, for use another time, while some was burned to run the machine. The sugar thus supplied both the piston and the gasoline. But difficulties were not long in appearing. How, for example, could a muscle use fat to run its contractions, for fat can produce energy but not lactic acid? Nonetheless, other chemical evidence proved that fat and still other substances *could* serve as fuel for the muscle engine. But the real scientific storm blew up when it was proved conclusively that muscles poisoned with a drug, iodoacetic acid, which entirely prevented the formation of lactic acid, could still contract perfectly well over quite a period. Obviously lactic acid was not a necessary part of the chemical

machine; perhaps it was but one of the interchangeable, energy-yielding reactions.

This has since proved to be the case. The reason that fermentation does occur, early and in large amounts, to be mostly reversed later by oxidation, is found in the necessity for speed. Cells have little store of oxygen within them and can, therefore, oxidize sugar only so fast as the blood is able to supply this essential gas. (This is true for muscle also, though "red" muscle has a special oxygen-holding pigment.) But fermentation requires nothing not already present in the cell and can proceed to liberate energy as rapidly as need be. Glycolysis serves, therefore, like available cash-on-hand, whereas oxidation is more like the reserve in the bank containing usually more but less available funds. We may safely carry this analogy further and speak of the muscle as going into an "oxygen-debt" by its rapid exploitation of glycolysis and as paying off the debt with its leisurely oxidations.

Phosphate compounds. Now some other chemical reaction is needed to set off the actual contraction. Fortunately, at about the same time that contraction without lactic acid was proved possible, two new substances were discovered in muscle, both of them phosphate compounds. (If you like names, they are creatinephosphate and adenylypyrophosphate.) Each splits off the phosphate part of the molecule during contraction and recombines it during recovery. Furthermore, both are rather strong acids in the combined form, whereas the molecules into which they break down are weaker ones; so that as they decompose the muscle becomes more alkaline. It has required ten years of incessant labor by hundreds of scientists to fill in this sketchy picture; but now we know that first one and then the other compound loses its phosphate, certainly within the time of a muscle twitch, and that the lactic acid formation follows afterward. However, the story is now quite complete and satisfactory, and there is even pretty good evidence (from the amount of change in osmotic pressure, which is a measure of the total number of molecules present) that no other still

undiscovered chemical reactions of any consequence remain to again upset the apple cart.

Nature is usually reasonably simple when we finally understand her, and it is easy to look back with scorn upon the groping blunders made in trying to reach this understanding. Yet while the chase is on each quarry is peculiarly elusive, and it takes a great mind to find the simple answer which solves a muddled and often seemingly insoluble problem. You may be more impressed by the statement that at least four of the Nobel prize winners of the last fifteen years were honored, in part or whole, because of their contributions to our knowledge of muscle chemistry.

OTHER PROPERTIES. So much, then, for the cell machinery that leads to muscle contraction. It will not be practicable, indeed with our present knowledge not possible, to make a similar detailed examination of the finer mechanisms whereby other cells and tissues perform their prime functions. But you may be quite certain, despite omission or ignorance on my part, that similar devices, equally complete and intricate and altogether elegant, underlie the actions of all of them. Nor have we exhausted even some of the most general chapters of our knowledge about muscle.

Functions and disturbances. Have you the impression, for example, that the only function of muscles is to produce movement or to maintain posture? Then why, as we become colder, do we keep our muscles more and more tense and finally erupt into uncontrolled shivering? Would the deep-running nerves and arteries be more easily injured, by claw or tooth, if the heavy layers of muscle which overlie them were absent? Do you think you would like man's looks as well if he were more literally reduced to skin and bones; or would you get so used to such covered skeletons that a muscular Apollo would appear horribly bloated? Or, turning back to contraction, how do certain drugs make a single muscle twitch last for minutes and others cause a complete paralysis? Where does the mechanism go awry in the diseases in which muscles

waste away? What occurs in that peculiar disturbance in which the muscles are particularly large yet excessively weak—all stated in the name pseudohypertrophic muscular dystrophy?

Strength and efficiency. Again, how great are the actual forces which muscles can develop; and how efficient are these machines in transforming the energy of their chemical fuel into useful work? It is interesting, for example, that about 40 per cent of the chemical energy is efficiently used by muscle, whereas the best steam engine has an efficiency under 10 per

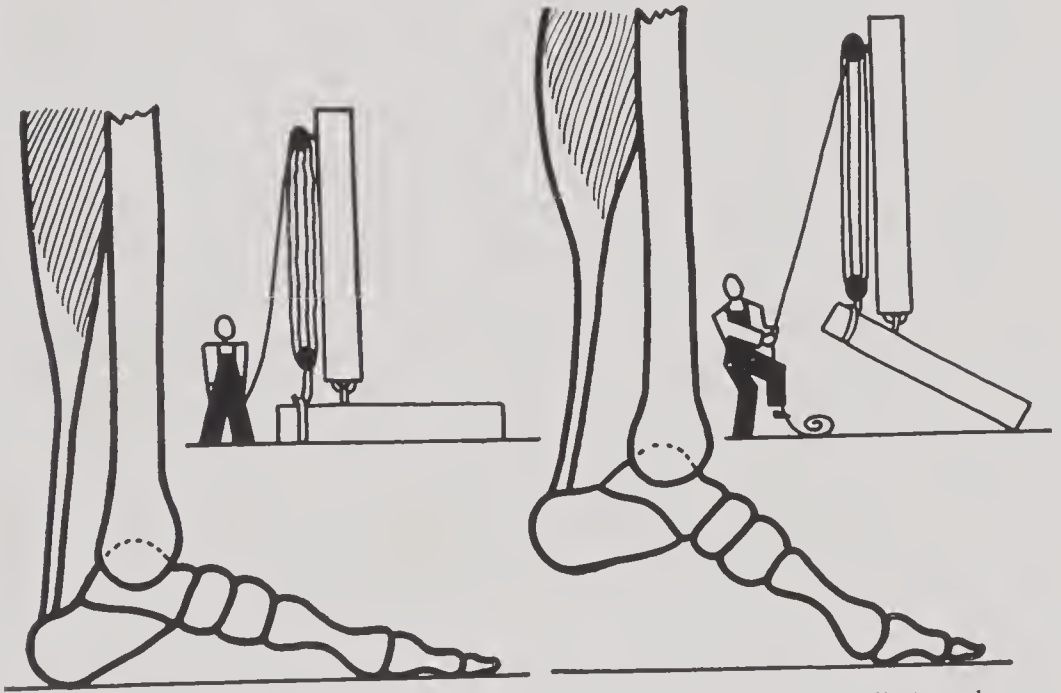


FIG. 12. Your calf muscle (gastrocnemius) pulling, through the Achilles' tendon, on the heel bone works against an adverse lever ratio of 6 to 1 when you lift yourself on your toes. (Drawn by P. McC.)

cent. Or, so far as strength is concerned, even we ordinary folk can throw out our chests a little. Any well man can raise himself on the toes of one foot, probably even while lifting another person. This means that his gastrocnemius muscle, contracting practically alone, is able to raise, say, 300 pounds. But the distance from the ball of the foot to the top of the arch, on which the body weight rests, is about six times the distance from this point to the heel bone, where the muscle attaches through the familiar Achilles' tendon. The muscle is, therefore, working against an adverse lever ratio of 6 : 1,

and it can directly lift, then, at least six times this actual weight, or practically a ton. Furthermore, because of regulation through the nervous system, a healthy person cannot voluntarily make any muscle give a single maximal twitch. This regulation breaks down in certain diseases of the nervous system; and then, when the gastrocnemius exerts its full power, it can rip its tremendously tough tendon or even tear off a piece of the bone to which it attaches!

So we must leave skeletal muscle, as indeed we shall have to leave every body part or process, with only a glimpse of the intricate and fascinating problems it presents.

OTHER KINDS OF MUSCLE

The other kinds of muscle, smooth and cardiac, are basically like the skeletal variety, yet show some striking differences.

SMOOTH MUSCLE. In smooth muscle, for example, the cells remain as individuals, each an elongated, spindle-shaped unit with its single nucleus and with no cross striations.

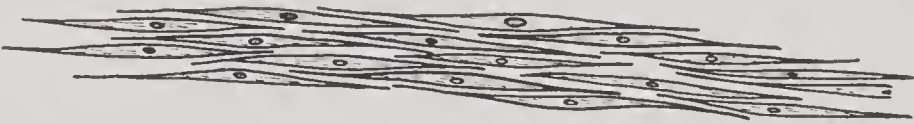


FIG. 13. Smooth muscle cells. (Drawn by P. McC.)

Of course they do not begin to achieve the dimensions of the striated fiber; but, arranged in parallel and fitting against one another, they form similar bands or sheets of muscle tissue. Since smooth muscle nearly always occurs in the wall of some hollow organ or viscus, as the stomach or urinary bladder or blood vessels, these muscular sheets have no attachment to bone but close upon themselves to form complete tubes or sacks. Sometimes, as on the blood vessels, the individual spindles lie curved as rings in the circumference of the tube. In other cases, as the gut, such a circular layer of muscle has added on outside a longitudinal second layer with the muscle cells all oriented along the length of the tube.

By simultaneous or alternate contractions of these layers,

the gut can squeeze out into a long tube, lump up into a short thick one, perform complex writhing movements, and execute its special peristaltic motion of traveling rings of contraction and relaxation. The earthworm is likewise supplied near its body surface with such sets of circular and longitudinal muscle. Watch one play itself like an accordion, send bulges and bottle-necks down its length from end to end, and twist and hump itself; and you will have a pretty good idea of the movements of your own intestines. Note also the rate at which these things happen; for one important difference between smooth and striated muscle is that the former contracts and relaxes

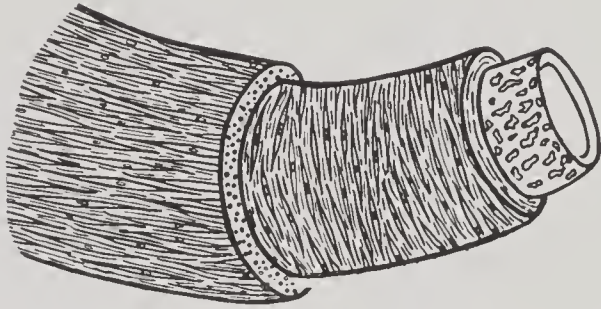


FIG. 14. Smooth muscle cells are grouped into bands or sheets in the walls of the hollow viscera. This diagram of the wall of the intestine shows the innermost layer of mucous membrane; the next layer of "circular" muscle in which the smooth muscle cells form rings, and on contracting narrow the gut; and another layer of "longitudinal" muscle which, on contracting, shortens and thickens the gut. A final outer covering layer of peritoneum is not shown. (Drawn by P. McC.)

much more slowly and may require seconds or even minutes for a single "twitch."

Another difference in activity is partly due to the way the nerve cells are connected. Those which control skeletal muscle are always far from them and act upon the muscle fibers through long extensions, whereas the nerve cells which help control smooth muscle are in part mixed with them. Whether for this reason or because of differences in the machinery of the muscle cells themselves, skeletal muscle at rest is completely relaxed but smooth muscle almost never. An isolated piece of intestine hung in warm salt solution shows regular rhythmic contraction and relaxation for hours or days; and when this is stopped in some way the muscle may come to rest contracted,

relaxed, or anywhere between. This may sound like contracture of skeletal muscle, but it is really quite different and is a perfectly normal state rather than an abnormal one. Your stomach, for example, is contracted down when empty into a small tube with practically no cavity present. Yet you can drop into it a pound of dinner in a quarter of an hour, or a quart or two of fluid (continental beer drinkers would consider this merely the opening sip) in a much shorter time, and the stomach keeps on relaxing so as to make a sack of just the right size to hold these contents.

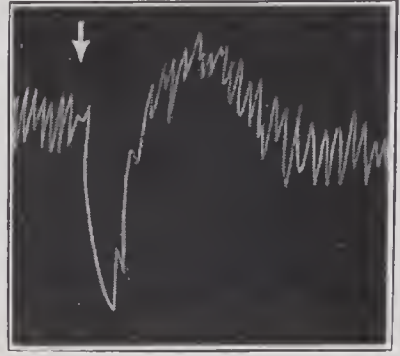


FIG. 15. This is the record obtained from a bit of rabbit intestine supported in warm salt solution with one end attached to a writing lever. Even when nothing was being done, the smooth muscle cells continuously contracted and relaxed to give a regular rhythm of about half a dozen beats a minute. (The drum was moving much more slowly in this experiment than in those with striated muscle.) At the moment indicated by the arrow, a minute amount of adrenalin was added to the solution and the intestinal muscles promptly relaxed to a far greater extent than during the normal beat, with maintained "tone." As the drug action disappears the original activity is restored.

CARDIAC MUSCLE. The cardiac muscle, which alone makes up almost the entire heart, is intermediate, both in structure and behavior, to the other kinds. It is striated, less regularly than skeletal muscle, and its cells are grouped into syncytial fibers. Fibers are shorter and more slender than those of skeletal muscle and are not packed as separate parallel threads. Rather, they run at slight angles to each other and, in fact, are not even separate, for they irregularly branch and reunite so that the entire heart is really one enormous interlacing muscle fiber. And how effective this peculiar arrangement is! The very nature of the heart's function demands that its entire cavity decrease in size by the simultaneous contraction (or increase by relaxation) of the muscle throughout its walls. The heart is a simple pump and must, therefore, act as a single unit. How much pressure would any pump develop if one of its walls bulged out as another closed in?

Like smooth muscle, but more rapidly and far more regularly, cardiac muscle maintains its repeated contraction and relaxation. The isolated heart, like the gut, can continue a practically normal beat for days; in fact it has been possible, by special care, to keep such a frog heart beating for over a month.

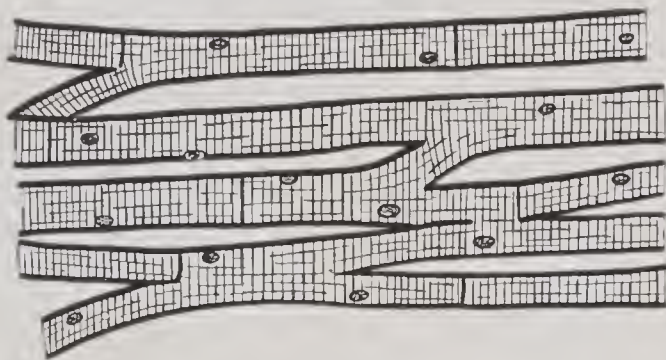


FIG. 16. The fibers of cardiac muscle are striated like those of skeletal muscle but are smaller, less regular, and branch and recombine with one another; so that truly the entire wall of the heart is one continuous fiber. (Drawn by P. McC.)

Unlike skeletal muscle, while the heart is contracting (called systole) it will not respond to a second stimulus; that is, it has a fairly long refractory period. But while it is relaxing (diastole), or during the brief pause before the next normal contraction, it can be stimulated in the usual way and then gives a premature

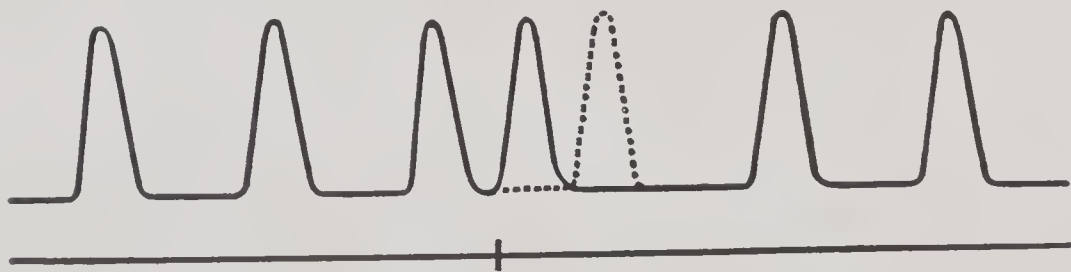


FIG. 17. An extrasystole of the regularly beating heart is produced by a stimulus at the time indicated on the signal magnet line. The next beat which actually occurs is indicated on the continuous line; that which would have occurred without the extra stimulus is dotted in. (Drawn by P. McC.)

beat (extrasystole). Following such an extra contraction in response to a single stimulus, the heart remains relaxed longer than normally, although a second stimulus applied during this relaxed period can cause another systole. Actually the time between the last normal beat before the extrasystole and the first normal beat following it is just twice the usual time

between regular beats. The normal beat that should have appeared half way between has failed to show up, following the extrasystole which preceded it (Fig. 17). You should now be able to draw some important conclusions as to the normal origin and control of the heart beat; try, and what we shall learn later will serve for comparison. From the facts—that the whole heart acts as one unit, and that it has a long refractory period so that summation of contractions is impossible—wouldn't you conclude that its contraction will always be all-or-none?

GLANDS

The other important effector we possess is the gland. If the muscles are the "laborers" of the body, the glands are the "cooks" and "caterers." Active muscles produce mechanical change; active glands, chemical change.

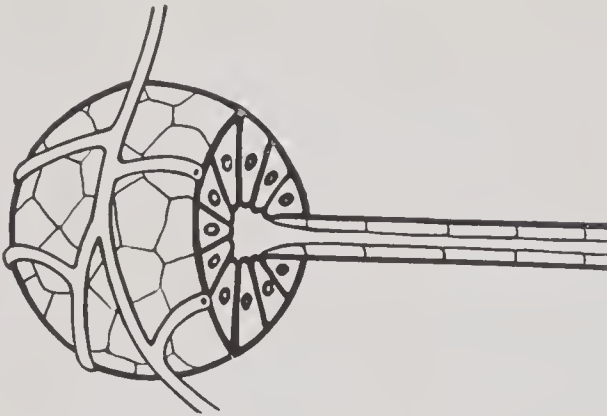


FIG. 18. The cells of a gland take substances from the blood passing in the capillaries on one surface and secrete these or other substances from the opposed surface into the lumen of the gland. (Drawn by E. M.)

GLANDS WHICH CONCENTRATE. Some, like the tear glands, merely transfer some water and dissolved substances from the blood to a new set of channels or ducts which empty the "secretion" onto a surface—that of the body or one of its hollow viscera. Tears contain little more than salt and water from blood and serve simply to moisten and wash the delicate membrane which covers the eye. Most of the sweat glands likewise serve essentially to spread a film of water on our skins which, by evaporating, cools them.

Even the kidney, that intricate and vital gland which forms the urine, normally contributes no new substances (or unimportant amounts of them) to the fluid which it passes through itself from blood to urine. It does, however, produce important changes in the relative amounts or concentrations of the dissolved substances which traverse it, far more than do the simpler tear or sweat glands. The kidney has the interesting job of picking from the blood those waste substances, like urea or uric acid, which accumulate in the body as end products of its incessantly swirling metabolism. At the same time it carefully leaves behind most or all of the many other substances mixed with them—the food molecules on their way to the tissues, messengers from one part of the body to another, salts, proteins, etc., which make the blood the peculiarly efficient bathing fluid for cells that it is. The small quantities of waste molecules dissolved in the large amount of water of the blood must be got rid of without the loss of much water.

The kidney's problem, then, is to pass into its ducts (and eventually, after a sojourn in the bladder, to the outside of the body) a small amount of water in which is dissolved urea, for example, in high concentration while the blood sugar, say, is completely held back. How this is achieved, by a neat microscopic filter followed by long tubules, we must examine later. But clearly the organ does work in the process of forming urine, for the molecules dissolved in it have been concentrated against osmotic pressure.* And so the kidney, like the muscle, has its own metabolism and burns its own food supply with oxygen in amounts related to the urine it secretes.

GLANDS WHICH MANUFACTURE. But most of the glands in the body—the large number of small finger-like burrows which dot the whole lining of the digestive tract; the special additional glands, such as the salivary glands, pancreas, and liver, which empty their secretions into the alimentary canal to aid in digestion; the various other small glands which

* Appendix C gives another bit of chemistry which will help you to understand osmosis and diffusion.

keep mucous membranes moist and slippery; even the endocrine glands, which pour their secretions back into the blood itself—do more than merely move chemicals from the blood into their secretions, for they manufacture new substances. These chemical products are usually large and complicated molecules; most are particular monopoly products of the one kind of gland that makes them; and many are powerful reagents, able to perform duties vital to the whole body. The juices of the digestive glands contain vigorous enzymes which tear apart food molecules and in the absence of which we should promptly starve; the endocrine glands make the many hormones so essential to health and even life; and so on.

This chemical synthesis also requires work and, indeed, the respiration of some of the endocrine glands, weight for weight, is higher than that of any other body organ. Even the massive liver uses oxygen ten times as rapidly as a like weight of resting skeletal muscle, though not so rapidly as an exercising muscle. But of how this energy is directed by the gland cells into the useful work of concentrating molecules already present or of building new ones, we know almost nothing.

To be sure, the structure of a gland is well adapted to its function. There are no large masses of solidly packed cells (except in glands which secrete their products back into the blood stream) but rather sheets of cells one layer thick with one surface richly supplied with blood vessels and the opposite one free. Since the secretion is emptied on this free surface, and must be collected from it into small ducts which join to form ever larger ones, the cell sheets are not stretched out flat. They are wrapped into cylinders, called tubules, or bent into tiny spheres, called acini, stuck on the ends of the ductlets like grapes on their stems. Materials enter the cells from the blood-vessel side, and the same or new substances leave the cells for the cavity or lumen which they surround; but the all-important events which occur within these cells remain still a mystery.

Many glands, like the muscles, are under the control of nerves which excite them to secrete. But many others are also

or only controlled by chemical messengers which reach them through the blood and which, like nerves, are able to increase or decrease their activity. These problems of the control of the effectors of the body must wait, however, until we have learned something more of the nerves themselves and of the sense organs, which start the whole process going.

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CHAPTER II

NERVES AND THE NERVE IMPULSE

CONDUCTION. All that we know of the world about us depends on our nerves, and so, for that matter, does everything we are able to do in the outer world. The nerves, strung through all the body, connect the sense organs to the central nervous system and this to the effectors. When one nerve is cut or has its action blocked in some other way, as by injection of a local anesthetic, the body part which it supplies, or innervates, is in effect cut off from the remainder. When the wire to a spark plug is disconnected, the cylinder doesn't work; when the nerve to a skeletal muscle is cut, the muscle is paralyzed. The dentist injects novocaine around the nerves from the teeth and, when it has taken effect and blocked them, all sensation from the teeth and gums is abolished and they feel "dead" and anesthetized.

The nerve, then, must be a pathway along which something travels; some message which informs the brain of sensation or makes a muscle contract, and one which is unable to detour when the road is blocked. Or perhaps we should not jump to conclusions and say "*a* message," for we have no right yet to assume that only one kind of impulse travels along nerves. We should have to prove first the rather surprising conclusion that a single kind of nerve message can lead to such widely different results as our feeling pain or seeing light or moving muscles or secreting saliva. Well, then, before we tackle the exciting but more difficult question of what travels along nerves let us learn something of the roadway itself.

NEURONES. If a spider, hanging just above the ground by its fine thread attached to the top of a six-story building,

were reduced in size about twenty times, thread included, it would rather resemble a nerve cell, or neurone. The main body of the nerve cell, with its nucleus and cytoplasm, is not unduly large or peculiar as cells go. It ranges up to about 0.1 millimeter in diameter and is shaped as an irregular pyramid



FIG. 19. In the two nerve cells shown the dendrites extend up and to the sides from the cell body, the axone runs down and out of the picture. The cell on the left is found only in the cerebellum, that on the right only in the motor part of the cerebral cortex. The cells constituting different brain regions are thus often as unique as are the functions of those regions. (The cell at the right is shown at several times larger magnification than is the other.) (Drawn by P. McC.)

or star. But the neurone does not stop with its cell body, as ordinary uninquisitive cells do, but sends out fine thread-like processes to explore far distant regions. Most of the processes extend for moderate distances, a few millimeters as a rule, and branch repeatedly, from fairly stocky stems to the finest of twigs. These dendrites, so called for their branching habit, may make quite a thick bush around the cell body. But one slender

process, often less than 0.01 millimeter in diameter, suffers from unbridled wanderlust and threads its course for centimeters or even meters away from its origin.

All the neurones of the regular nervous system are gathered together in the central brain and spinal cord, of which they form the gray matter. (A special, partly separate, nervous system, called the visceral or autonomic system, has its cells scattered about the body.) Only their long processes, the axones (from axis), connect them with the rest of the body. Bundles of these axis cylinders, coming from related cells, make up the nerves. These fiber bundles, incidentally, whether running between nervous system and peripheral parts or as long tracts connecting well-separated parts of the central nervous system with each other, are white rather than gray. Their glistening pearly appearance is due to a special fatty substance, myelin, which is neatly wrapped around most individual axis cylinders like rubber insulation around a wire.

Have you become sufficiently scientific to have asked yourselves, "How can he be so certain that these long axones are really part of a single cell?" Perhaps you assumed that a competent biologist could simply look at the nervous system through a microscope and see this. But when you remember that tissues are killed, hardened, stained, and cut into microscopically thin slices like a delicately carved sausage, you will see how impossible it would be to trace the axone of a single cell through thousands of such sections. Actually, a major scientific war was fought for half a century over the question of whether or not axones really are part of nerve cells. The final proof was supplied only thirty years ago, by the clever experiment of placing bits of embryonic brain in a sterile food-containing liquid outside the body (the method of tissue culture) and watching the young neurones develop. The processes could then be seen growing out from individual cells like a root from a potato. But even before this final proof, other evidence had been obtained which also helped neurologists to do what seemed impossible—to trace the courses taken by axones from particular cells.

NERVE PATHWAYS. You will recall that any part of a cell, for example of an amoeba, cut from the remainder which contains the nucleus, eventually dies and degenerates. The same is true for a neurone's processes; for when a cut is made in a nerve or in the central nervous system, parts of

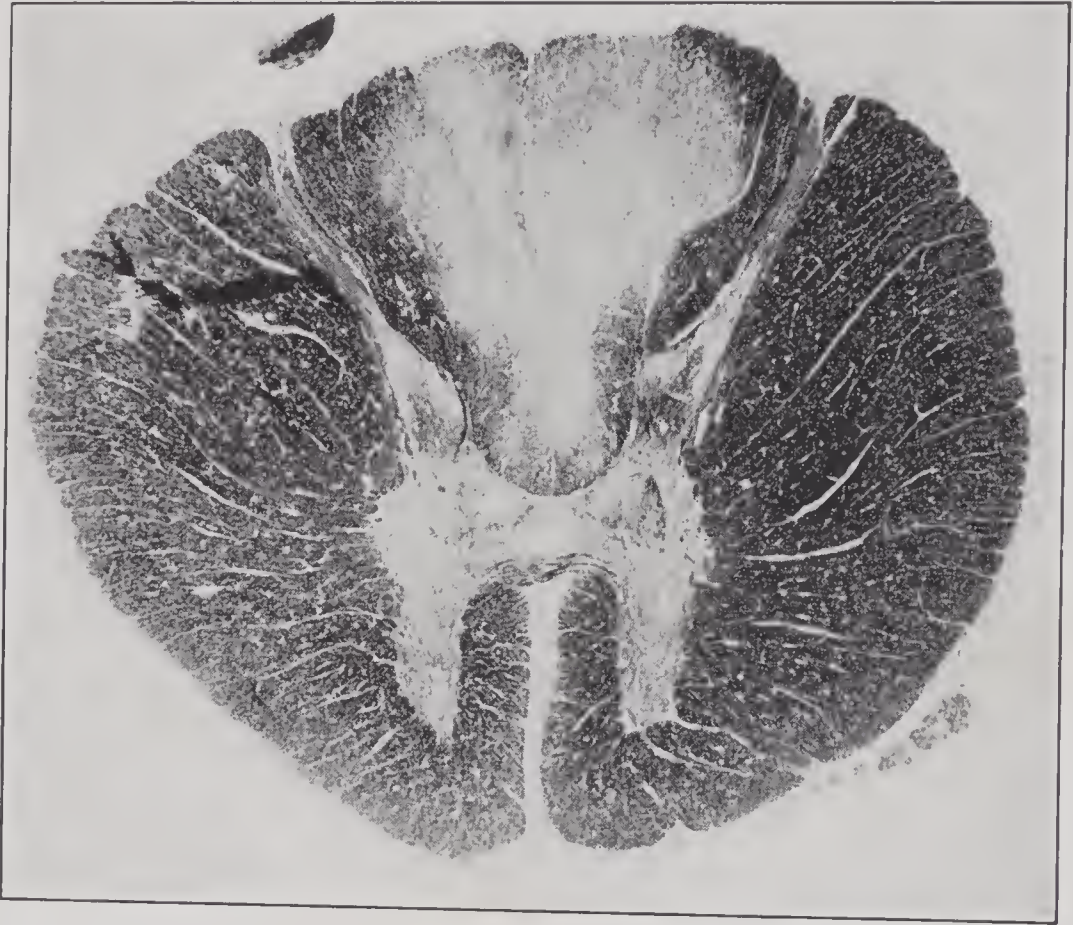


FIG. 20. This transverse section of the spinal cord has been stained by a method which blackens the normal nerve fibers. The H-shaped "gray" matter remains pale since it contains mainly nerve cells without myelin. The wedge-shaped patch of white at the top of the picture shows a mass of nerve fibers which has degenerated as a result of syphilitic infection, and so does not stain. (From Grinker's *Neurology*, Second Edition. Courtesy of the author and of Charles C. Thomas, publisher, Springfield, Illinois.)

some axones are separated from their cell bodies, and these isolated fibers degenerate. In a few days the myelin of the injured process has become so changed chemically that it reacts with new chemical reagents and, for instance, reduces osmic acid to a black insoluble substance. By making small cuts in known parts of the nervous system, waiting for degenera-

tion, and then fixing, slicing, and treating with osmic acid, the degenerated fibers are accurately located as black spots. The procedure is rather like developing the black silver deposits where a photographic plate has been exposed to light. Mainly by this means, the unbelievably complex network of nerve fibers interconnecting all parts of the nervous system has been very extensively unraveled—a stupendous task requiring the devoted life work of many neurologists. Think of the main

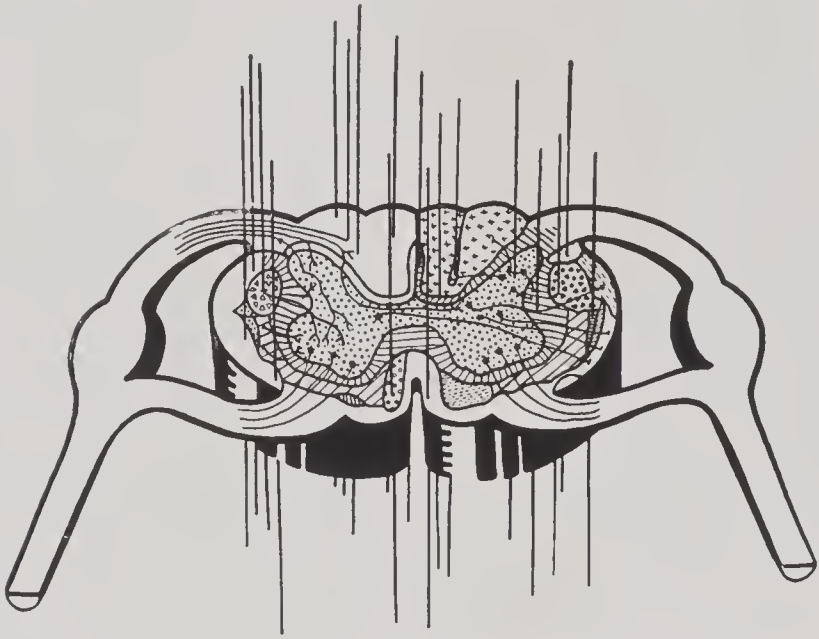


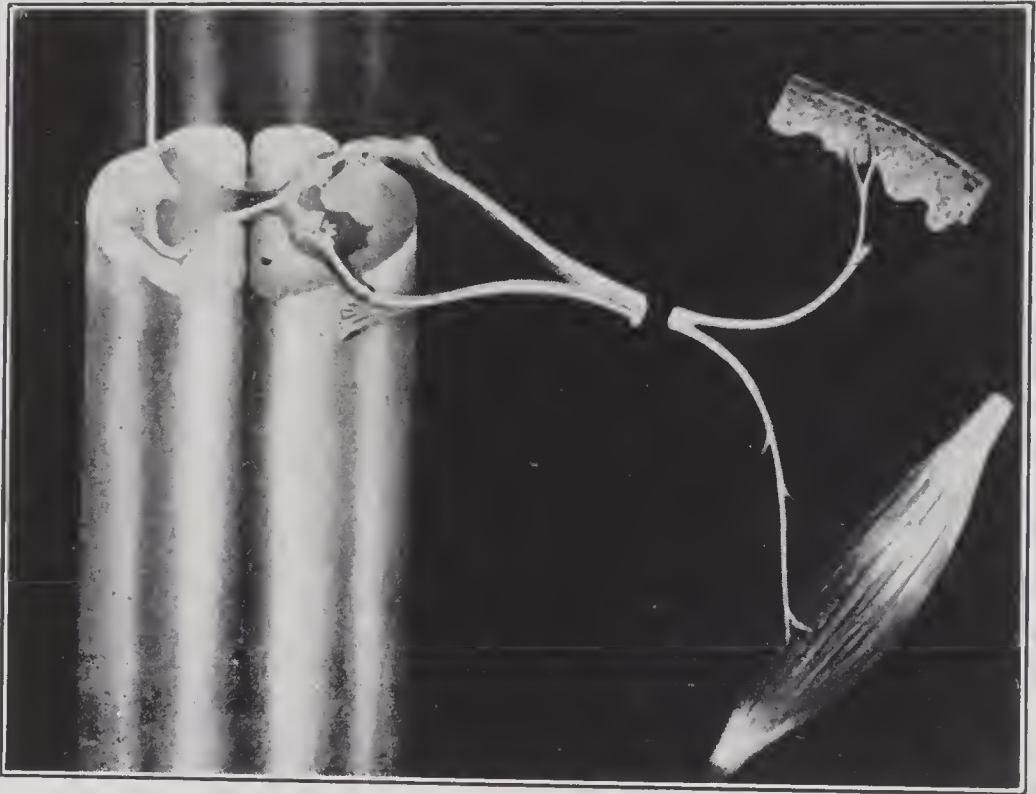
FIG. 21. In this diagram of a section of spinal cord (with the dorsal and ventral roots on each side shown joining to form peripheral nerves), the central butterfly-shaped stippled area is gray matter, the remainder white. Different bundles of fibers in the white matter, which run between fixed regions above and below, are indicated by the various kinds of texture. A few individual nerve cells or fiber connections are indicated. (Drawn by P. McC.)

telephone exchange of a large city shrunk to the size of a watch, and yet tracing the circuits in it! Every line in Fig. 21 represents a nerve path that has been carefully mapped in this manner; and only a few of the most important ones are shown, else the almost-solid black tangle would be undecipherable.

Fortunately, the cell which has lost its axone (as when nerves are cut by deep wounds) is able to grow a new one, as a tadpole can regenerate a tail. After some months or even years, the central end of a cut nerve, that connected to the

nervous system, has regenerated along the dead peripheral path, still connected to the innervated organ, and has restored function to the paralyzed muscle or gland, or to the anesthetic sense organ.

Individual nerve cells make contact with each other through their processes, the axone of one meeting the dendrite of



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FIG. 22. This diagram shows a nerve fiber coming from the skin and entering the gray matter of the spinal cord through the dorsal root. The cell body of this neurone is in the ganglion or swelling of the dorsal root. In the gray matter it synapses with another neurone, which sends one branch across the cord into a nerve tract running towards the brain and a second branch to synapse with the motor neurone in the ventral part of the cord. This latter sends its axone through the ventral root to reach a muscle and so completes a simple reflex arc. (From the film, *The Nervous System*, by Gerard.)

another. The region of junction, called the synapse (coming together), allows the nerve message, which has been traveling along the axone, to continue on into the dendrite of a second cell. But passage across a synapse is not so simple as travel along one fiber. A nerve impulse, however started, will run in whatever fiber it finds itself, follow it to synapses with other neurones, pass certain of these—the basis of selection we shall

see later—and so be carried to more or less determined parts of the nervous system or back out to the periphery of the body.

Thus, a prick to the skin of the foot excites the pain sense organs there and starts nerve impulses along the sensory, or afferent, nerve fibers connected with them. These nerve fibers belong to particular cells in the spinal cord which synapse with other definite cells near them. These in turn synapse with still others, the axones of which run from the cord in motor, or efferent, nerves to the muscles which flex the leg. Other branches from the sensory neurones run up the length of the cord and connect with other neurones, eventually reaching the brain. Nerve impulses arriving there give us knowledge of the prick; but even when the spinal cord is cut across, so that no sensation is possible, the connections in the cord still work and the contracting muscles pull the foot away from the disturbing prick. This automatic reflex behavior is, therefore, the result of nerve impulses traveling along previously laid down tracts. In these neurone patterns and their unthought, yet highly effective, inherited behavior lie some of the greatest triumphs of evolution and some of the highest peaks of living performance. But this story must wait while we examine the traffic which travels these highways.

THE NERVE IMPULSE. The scientist, in his professional capacity, refuses to deal with phenomena or objects which he cannot measure or at least observe. Only by noting the answers which nature makes to definite questions, and by framing his further questions accordingly, can he drive his impersonal witness to reveal more and more about herself.

The problem of measurement. To study the nerve impulse we must have some index or measure of it; the absence of obvious signs of its passage kept it mysterious for centuries. True, when the frog's gastrocnemius and the sciatic nerve attached to it are dissected out, the muscle will twitch each time the nerve is irritated, even at its far end over six centimeters away; so that the muscle response can be used to test whether or not something has traveled along the nerve.

But, when the muscle is gone, one can watch the nerve itself, even through the microscope, and see absolutely no change on stimulation. Further, attempts to demonstrate, by measurements of heat production, oxygen consumption, or chemical change, that the nerve increases its metabolic activity while it is conducting impulses were until quite recently completely unsuccessful.

No wonder, then, that physiologists thought of nerves as inert pathways or conductors which merely allowed the excitation imposed upon them at one end by the stimulus to pass along to the other. Water flowing through a tube or electric current moving through a wire—to say nothing of automobiles rolling along a highway—do not depend on any active contribution by the channel along which they travel. The amount of water flowing, its speed, how it pulses, the pressure it exerts, vary with the pump forcing it through the pipe; and the nerve impulse, long thought to be the flow of a fluid of special virtues, called animal spirit, along invisible pores in the nerve, was supposed to behave quite similarly. Such interesting but useless fancies result when even the finest minds attempt to guess too far ahead of available evidence.

Electrical changes and velocity. The beginning of our actual knowledge was nearly a century and a half ago when Galvani, while watching frog legs hung from an iron fence by a copper wire hooked under the sciatic nerves, accidentally discovered that whenever the wind-blown legs touched the iron the muscles twitched. The contact of copper and iron made a feeble battery, and when the frog tissues completed the circuit a current flowed and excited the nerves. Thus was discovered simultaneously a means of producing steady current, known to this day as a galvanic current, and the important fact that electrical currents can excite nerve. It was fully fifty years later, when the electrophysics which flowered from Galvani's work had produced sensitive galvanometers (also named for him) and other electrical apparatus, that another physiologist showed that nerve and muscle (really practically any tissue) not merely can be stimulated by electricity but, far more

instructive, actually produce electrical currents when they are active, no matter how stimulated.

This discovery set the scientific world agog, for the conclusion was promptly drawn that the nerve impulse is an electric current; and since electricity was by then known to travel at an enormous speed, it was confidently predicted by Müller, a leading scientist of the day, that, in the short lengths of nerve available, it would forever be impossible to measure the velocity of the nerve impulse. Yet Müller's own student, Helmholtz, one of the towering intellects of all time, measured the velocity of the nerve impulse less than a decade later—and less than a century ago—with almost as great an accuracy as we know it today. (I have said that the teacher was a great scientist; is it necessary, then, to add that he was delighted with his student's great achievement even though it proved him wrong?) Really it was not so difficult to make this measurement, for the actual speed is the very moderate one of 30 meters a second, a mile a minute, in frog nerve, and some four times this in our own.

You can measure it yourself with a little trouble, much as Helmholtz did. Place one pair of wires, to deliver an electric stimulus, on the nerve near the muscle, a second pair on its far end, say 6 centimeters away. The muscle will twitch in response to a stimulus applied at either position; but when the far electrodes are used the twitch will start later than when the near ones are used by just that time which the nerve impulse consumes in traveling the extra 6 centimeters. The time difference, given the speed we now know, will obviously be 0.002 second. The muscle lever is made to record each contraction by scratching a white line on a smoked paper, moved past the lever point sufficiently quickly. If the paper is started at the same place on each test, and the stimulus delivered at the same time, the later contraction curve will be displaced on the record compared to the first. From the known rate of movement of the paper, say 100 centimeters per second, and the distance of this displacement * the velocity of the nerve impulse is obtained (Fig. 23).

* Which would be how much for the known speed?

This experiment clearly proved that the nerve impulse is not simply an electric current, it moves far too slowly; yet it remained indubitably true that an electrical change does accompany the nerve impulse. It was soon shown, by moving a measuring electrode to different positions along the nerve while still stimulating at one end, that this electrical change, or action potential as it is called, moves along the nerve at exactly the same speed as does the nerve impulse. Of course,

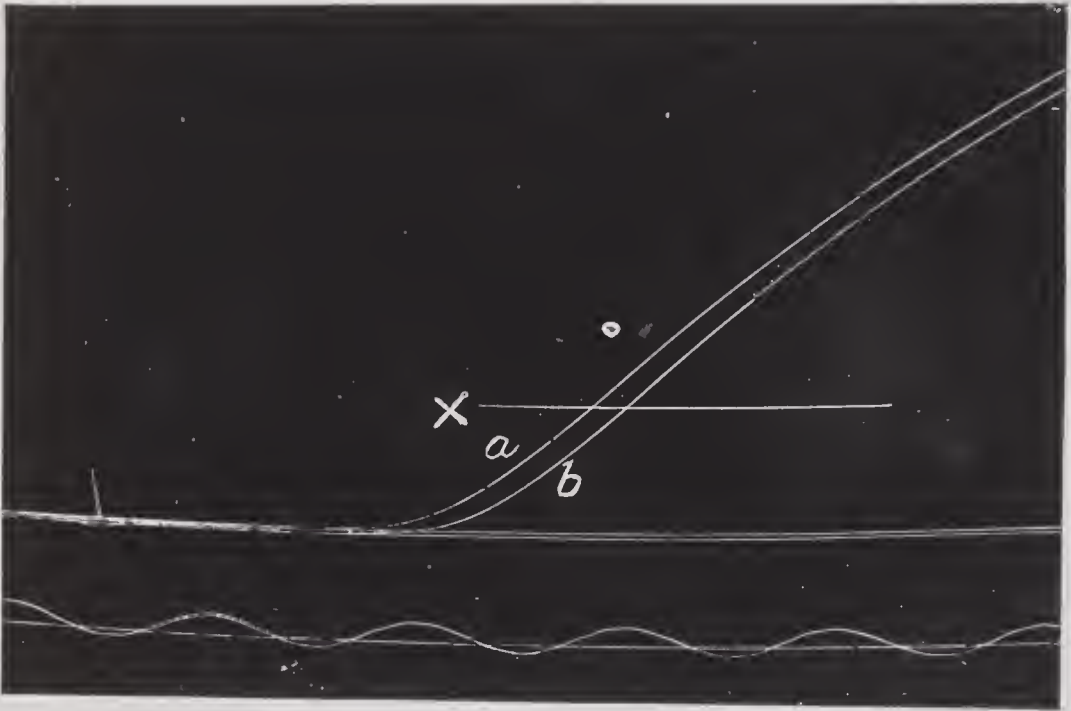
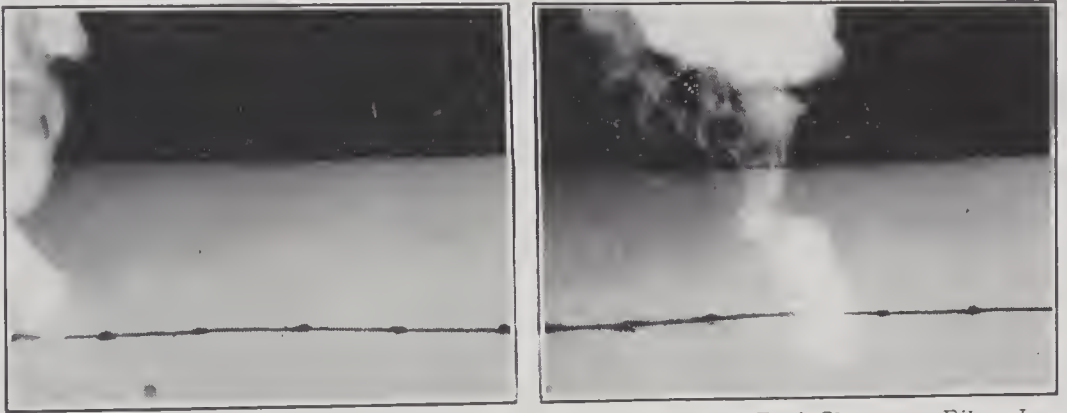


FIG. 23. An actual record of two muscle twitches, produced by stimulating the nerve near to (*a*) or far from (*b*), its entrance into the muscle. The wavy line at the bottom was made by a tuning fork vibrating 100 times a second. The record reads from left to right. (Howell's *Textbook of Physiology*, W. B. Saunders Company.)

the action potential might travel with the nerve message and yet, like the noise of a moving automobile, be an accidental and unimportant phenomenon. But many other experiments have shown that the action potential invariably accompanies the impulse; that its intensity, shape, and other characteristics accurately parallel the intensity and other attributes of the nerve impulse, as measured by different criteria; and that, in fact, the electrical change is an integral part of the impulse itself.

Here, then, we have at last the index so sorely needed; and the nerve impulse can be studied in detail by accurate measurements of action potentials, which modern radio amplifiers and oscillographs make possible.

Propagation is active. The mere fact that the active nerve generates electricity throws doubt on the view that the nerve is simply a passive conductor. The individual nerve fiber must actively contribute to propagating the impulse; and, indeed, very delicate measurements have proved in the last dozen years that the nerve conducting messages does increase its metabolism, just as does contracting muscle or secreting gland,



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FIG. 24. Two frames from a motion picture showing a flame burning its way along a train of gun powder from left to right. (From the film, *The Nervous System*, by Gerard.)

although the actual increase in nerve is only about one-thousandth as much as that in an equal weight of muscle. As the impulse travels, then, one point after another along the fiber shows electrical and chemical changes. If a short stretch of nerve is depressed, by cooling or by applying anesthetic or other drugs, so that it produces no or subnormal electrical and chemical changes, the impulse simply stops when it reaches this part of the nerve. Each region, therefore, when it becomes active, must somehow excite the following still resting region to become active, this the next, and so along the whole fiber.

We are thus brought back to a picture resembling the burning fuse. Think of the fuse as a nerve fiber, of the spark

moving along it as the nerve impulse, and you can understand, and even predict, much of the behavior of nerve. When a fuse is lit (stimulated) a chemical reaction which produces heat is started at that point. The next portion of the fuse gets warmer and warmer until it suddenly ignites (responds). The same chemical reactions are repeated, more heat is liberated, a third region is warmed and ignites, and the spark travels smoothly on its way. Of course in the nerve it is not the heat produced by an active region which stimulates the part ahead—the active nerve increases its temperature only a ten-millionth of a degree—but it is actually the electrical currents, as we shall see, which do this job. The fundamental similarity in the two cases, fuse and nerve, however, is that each part is stimulated by the preceding one, becomes active, and in turn stimulates the succeeding one. A wave of chemical and physical change moves along the structure, to be sure, but what is really passed on from point to point is the excitation itself. The nerve impulse has, in fact, been defined as “a propagated tendency to excite,” and you can see now that this is a pretty good definition.

The all-or-none law. Now, whatever the mechanism by which an active region stimulates its neighbor to like activity, certain important consequences follow. The original stimulus, once it has set off the first region, is completely out of the picture; the further fate of the nerve impulse—its strength, its speed, its further travel—depends at any moment only on the condition of the region in which it is at that moment. The spark similarly travels down the fuse in just one manner, whether started by a match or a blow torch. When a stretch of the fuse is wet, the spark goes out on reaching it; if only damp, the spark may still pass through this region, but more slowly and as a feebler conflagration than when in the dry portion. If the spark gets through the damp spot, however, to reach the dry portion beyond, it fully regains its normal speed and intensity. In exactly the same way, the nerve impulse is quite independent of the strength or nature of the stimulus which starts it, if only the stimulus is strong enough to excite,

but it is dependent at each moment on the condition of the nerve in which it is traveling. The impulse also is blocked when it reaches a severely depressed stretch of nerve, is slowed and enfeebled in a moderately depressed region, and is again restored to normal when it passes on into the unchanged nerve ahead. This decrease of speed and intensity in a partially anesthetized stretch of nerve has been demonstrated by measuring the action potential, not only in a whole nerve trunk but even in one single nerve axone.

This is the important all-or-none relationship which earlier we encountered in connection with skeletal muscle, and it is equally true for the transmission of excitation throughout the heart or along a skeletal muscle fiber. The propagated wave



FIG. 25. The intensity of a nerve impulse traveling from left to right along a nerve fiber is indicated by the height of the action potential outlined above the fiber. Past positions of the impulse are dotted. The slightly shriveled region of the fiber indicates the depressed portion in which the impulse intensity is reduced. (Drawn by P. McC.)

of change is independent of its past history; the particular region active at any moment gives the maximal response of which it is then physiologically capable—it gives its all. There are some surprising consequences to this relationship, and it raises some interesting questions. How, for example, could you account for a strong prick hurting more than a weak one, or an intense light looking brighter than a dim one, if the nerve message is so entirely independent of the strength of the stimulus which started it? Worry about this for a while.

The refractory period. The fuse has still more to teach us. We know the answer as soon as we ask: “How soon after one spark has burned its way along can a second one follow?” Never, in the fuse; and certainly, in the nerve, a second impulse cannot immediately succeed a first one. The fuse is dead and cannot recover when burned; the nerve is living and might reset itself, but this must inevitably take time. We

saw in muscle that relaxation is a more important and difficult achievement than is contraction; in nerve, likewise, recovery of the ability to conduct new impulses, after going all out in conducting a first one, is the greater achievement. And how skillfully the nerve does this! For perhaps 0.002 second after an impulse has passed, the nerve is absolutely refractory, quite unable to conduct; during the next 0.01 second it is relatively refractory, has recovered enough so that it can be stimulated with sufficient effort, and transmits a slow and feeble impulse. By the end of this brief time, however, the mechanism for conduction has been completely reset and a full-sized impulse can travel. Extra respiration and other metabolic changes continue, however, again as in muscle, for half an hour or longer and prove that the nerve requires at least this long to be really restored to its resting state.

Stimulation. A nerve fiber, we have seen, can be stimulated, by electricity, heat, chemicals, pressure, or what-not, anywhere along its length—obviously, if the nerve impulse is a propagated excitation, every point must be irritable—but normally a nerve impulse never starts in this way. To be sure, a nerve trunk is occasionally stimulated—as when you knock your “funny bone” or when salt or acid gets into an open wound—but such experiences, although real enough, are hardly normal. The usual stimuli act on sense organs, which set up impulses at the end of a nerve fiber; and other neurones are excited at their dendrites by impulses which reach them through the synapses. Any particular sensory or motor nerve, therefore, conducts impulses only towards or only from the central nervous system. It was long believed that a fiber could conduct an impulse only in the one direction normal for it; but what does the all-or-none relation, or the fuse, tell us? Of course the impulse conducted backwards (antidromic) would not reach its usual connection to produce some response, and it could not, therefore, be detected until a measure of the impulse itself was available. But action potentials do prove that exactly the same kind of impulse goes in both directions from the point stimulated—as it should.

Only one kind of impulse. We can now return to the question left hanging earlier: Do vision, hearing, movement, etc., depend each on a different kind of impulse, or does just one kind produce any of these different effects, depending on the place it reaches? The all-or-none relation requires that any one nerve fiber can conduct only one kind of impulse, whatever the stimulus that started it; so the only way in which different kinds of impulses could exist and so bring about different sensations or actions would be by having a different kind of nerve fiber to carry each. Yet, by all the tests we have, the messages traveling in all sorts of nerves are the same. Not identical, to be sure, for some fibers conduct, for example, more rapidly than others; but as like as peas. Further, various nerves can be cut and the central end of one sewed to the peripheral end of the other, so that the fibers coming from the nervous system in trunk *A* regenerate along the distal part of trunk *B*, and vice versa. A nerve which originally connected with the diaphragm can thus be made to innervate a muscle in the arm or in the eye; and these muscles respond perfectly well to impulses coming down the nerve.

Even more, nerves from the various sense organs can be crossed. If the quality of a sensation depends on a special impulse, then, with the ear attached to the optic nerve, sounds might still be heard; but, if the quality depends on which part of the brain the impulses reach, then they should be seen. Experiments of this kind are obviously difficult, yet there is evidence that the latter is the case.

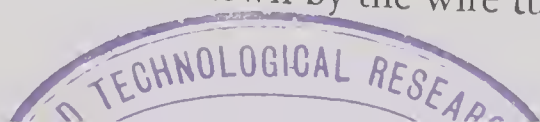
This much, at least, is very simply demonstrated concerning the importance of location in the brain: whenever the optic nerves or the parts of the brain to which they go are stimulated—by pressure, electricity, etc.—there results a sensation of light. Try it on yourself. Arrange several dry cells to deliver about twenty volts and connect them through two copper wires, the free ends of which are coiled around a cotton pledget soaked in a salt solution (about 1 per cent). Place one cotton electrode an inch or so above and behind each ear, so that the current can flow through the brain between them, and then

open and close a key in the circuit. Each time the current starts or stops you will have the pleasure of seeing "stars" without the painful bump usually used to produce them.

How nerve impulses reaching this particular part of the brain produce sensations of vision, while like impulses reaching another part a little further forward produce sensations of hearing, we have at present not the slightest idea. This is one of the most fundamental of all problems of living things, and there is no reason to suppose that it cannot be solved. Perhaps some day, if you should become a scientist, you may help to reach its solution.

A nerve model. Here we are chasing nerve impulses all over the brain when we have, as yet, only the vaguest notion of what they are. The fuse gave us a good working picture, but it fell down badly as a model because propagation in it depends on heat and because it doesn't recover after one excitation has traveled along it. A recent model does far better and behaves like nerve in so many details that it is almost certain that similar mechanisms are at work in the two cases. If you are careful not to spill acid, you can play with an artificial nerve in the laboratory, or even in the kitchen.

Take a straight piece of iron wire (piano wire is ideal) or a slender iron rod, half a foot to a foot long; support its ends on bits of clay or glass in a porcelain or glass dish, and cover it with nitric acid (70 volumes of concentrated acid plus 30 volumes of water). The iron starts to dissolve furiously, but soon stops and lies inactive in the acid. It now looks almost silvery, because of a very thin layer of iron oxide which surrounds it. It is this film or membrane of oxide which prevents the acid from further dissolving the iron under it. If, now, one end of the passive wire is "stimulated," by scratching off the membrane with a piece of broken glass (or by reducing it at the negative electrode of a current applied through two acid-resistant wires, for example platinum), the inert wire becomes active. You can easily see what happens. Starting at the stimulated point and spreading fairly rapidly along the wire, a wave of chemical action is shown by the wire turning brown



and by bubbles of gas arising from its surface. Only one wave travels; for, following along right after the active region, the oxide membrane reforms and the wire is left passive as before. There is a brief refractory period, and after this the wire can again be stimulated and again transmits one impulse.



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FIG. 26. This photograph of an iron rod standing upright in a cylinder of nitric acid shows the rod blackened in the upper portion by a descending wave of activity. This iron-wire system is a remarkably good model of a nerve fiber carrying an impulse. (From the film, *The Nervous System*, by Gerard.)

Now how does it work? The exposed iron, at the point where the oxide was scraped off, is electrically different from the oxide membrane. The two constitute a tiny battery, and current flows out from the iron, through the acid, back in through the oxide, and along the iron core. But such a current oxidizes the metal surface that it leaves and reduces the surface that it enters. The exposed iron thus becomes covered with fresh oxide, while the oxide membrane near it is reduced* to iron. The same currents can then flow between the freshly exposed iron and the oxide membrane still beyond; and the process repeats itself until the wave of activity and re-passivation has traversed the whole wire. Here, then, it is an electric current, flowing between the excited and the still resting regions, which

stimulates the latter; and the wire behaves so much like the nerve because electric currents, the action potentials, play this same role in the nerve fiber.

The mechanism of propagation. How, finally, is the impulse actually transmitted in the nerve itself? Each axone is

* Oxidation is the addition of oxygen atoms to a molecule or, what amounts to the same thing, removal of hydrogen atoms. Reduction is the exact reverse—removal of oxygen or addition of hydrogen.

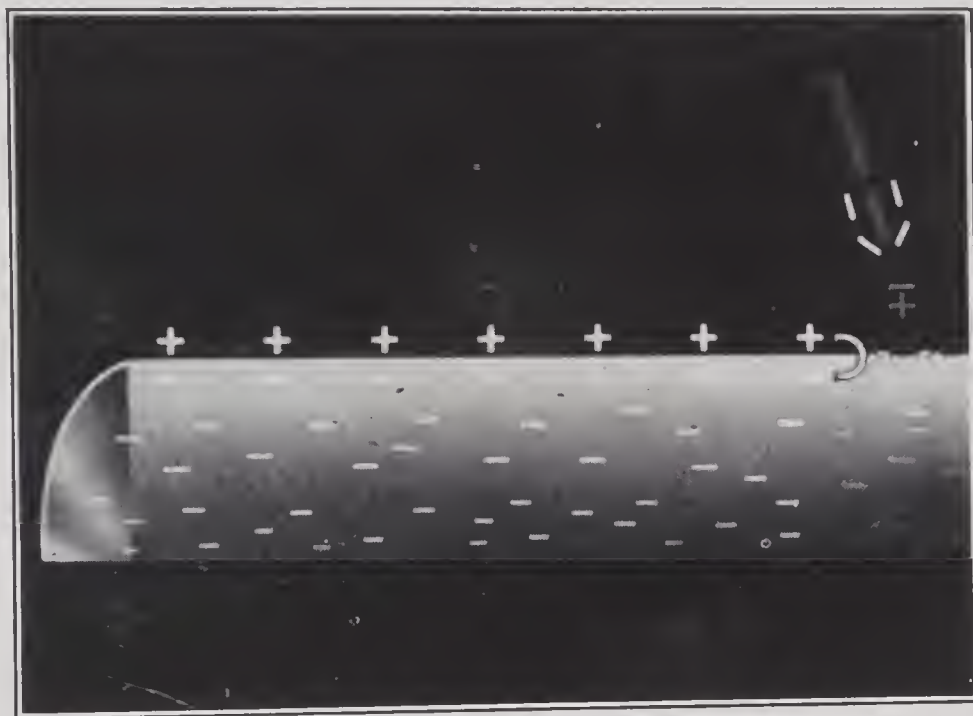
surrounded by a membrane, as is all protoplasm in cells. This membrane prevents many ions from passing through it; for nerves can be bathed in solutions of various salts without exchanging ions between the fluid within the axones and that outside. The semi-permeable membrane, further, is somehow kept by the nerve metabolism (for it requires work to do this) in a polarized state. Polarized means that an extra number of ions of one charge remains on its outer surface, a like excess of ions of the opposite charge on its inner surface, rather like a charged condenser. They do not mix and neutralize each other because the impermeable membrane is a non-conductor and does not let them through.

Actually, there is an excess of positive ions outside and of negative ones inside and the potential across the membrane may be 0.03 to 0.06 volt. We know this because when the nerve is injured at any point, so that the ions can mix, this region becomes less positive than the outside of the uninjured nerve, and a current flows between them. We know, further, that when the polarization of the membrane is removed, as by passing a current across it, the membrane becomes more permeable and, for a brief time, allows ions to cross.* Now we have all the facts necessary—and remember these are experimentally demonstrated facts—to understand how the nerve impulse propagates.

The membrane is depolarized at one point by the stimulus, the ions keeping the adjacent portion of the membrane polarized can now flow through the depolarized and permeable region, the second region thus becomes depolarized and permeable, a third region can now depolarize itself through the second, and away we go. Probably some chemical reactions occur in the depolarized membrane which make it permeable, and certainly such reactions occur during the refractory period and later, while the axone again charges up its membrane and repairs its insulation. Despite many additional

* Will the membrane be depolarized under the negative electrode or the positive electrode when these are placed at separate positions on its outer surface?

details, this electrochemical spread of excitation is really accomplished by an amazingly simple mechanism. On these feeble currents and tiny chemical changes are built the entire performance of complex animals and all the experience and creative thinking of the human brain.



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FIG. 27. This diagram of a longitudinal quadrant of a nerve fiber shows the positive charges on the outside of the membrane (visible only at the top) and the negative charges on the inside. A negative electrode applied at the right-hand side has caused the positive and negative charges to move away from the surface and become neutralized. The depolarized membrane has broken down, as indicated by the wavy dotted line, so permitting the positive and negative ions polarizing the next segment of membrane to flow through it as indicated by the white curve. As this second region is depolarized and broken down, the region yet beyond will discharge through it in like manner, and the nerve impulse so move forward. (From the film, *The Nervous System*, by Gerard.)

JUNCTIONAL TRANSMISSION. We have yet to learn how nerve impulses get started, which carries us into the large field of sense organs and excitation, but we can sneak up on this through certain special cases. A muscle or a gland is excited when nerve impulses reach it, to be sure, and the message which spreads along the membrane of the muscle fiber is quite comparable to that in the nerve. But how does the stimulus pass from the end of the nerve to the muscle,

across the axone's special flattened-out ending attached to the muscle unit? The same problem can be raised concerning the spread of activity from one neurone to another, across the synapse, and within the sense organs themselves, for usually special cells receive the external stimulus and must somehow excite the nerve fibers which lie among them. The myoneural junction, the synapse, and the receptor-neural junction might all use an identical mechanism for transmitting excitation from one unit to another or each might use a different one or several alternates.

We are not now certain of the answers to these questions, but this problem of junctional transmission is being carefully studied in laboratories all over the world so that by the time you read this we may be certain. Until a few years ago no one doubted much that the currents swirling along the nerve to its end simply excited the next structure as if it were a continuation of the nerve fiber itself. There is excellent evidence that this does happen often. But meanwhile another mechanism of transmission has been discovered and it also is certainly active in some cases. The uncertainty that exists is more a matter of the relative importance of the electrical and the chemical mechanisms in particular cases. They are, in fact, closely related; and when we recall that, even within the nerve fiber, transmission depends on both these factors it will not be surprising if, at particular endings, now one, now the other, dominates.

Chemical agents. Now what is this chemical mechanism at which I have been hinting? Here are the facts. The isolated frog heart, we have seen, can beat without stimuli through its nerves; yet two sets of nerves do go to it in the body and, when stimulated, they markedly affect its beat. One set, called accelerators, makes the heart beat faster and more powerfully; the other set stops it completely. These inhibitor nerves, the vagi,* are especially interesting because of their ability to

* The accelerators come from the cervical sympathetic nerves, the inhibitors from the right and left vagi. Each vagus nerve wanders around to reach nearly all the viscera, hence its name which means "wanderer." We shall hear much more of both kinds of nerves in the next chapter.

stop action rather than start it. This unexpected effect on

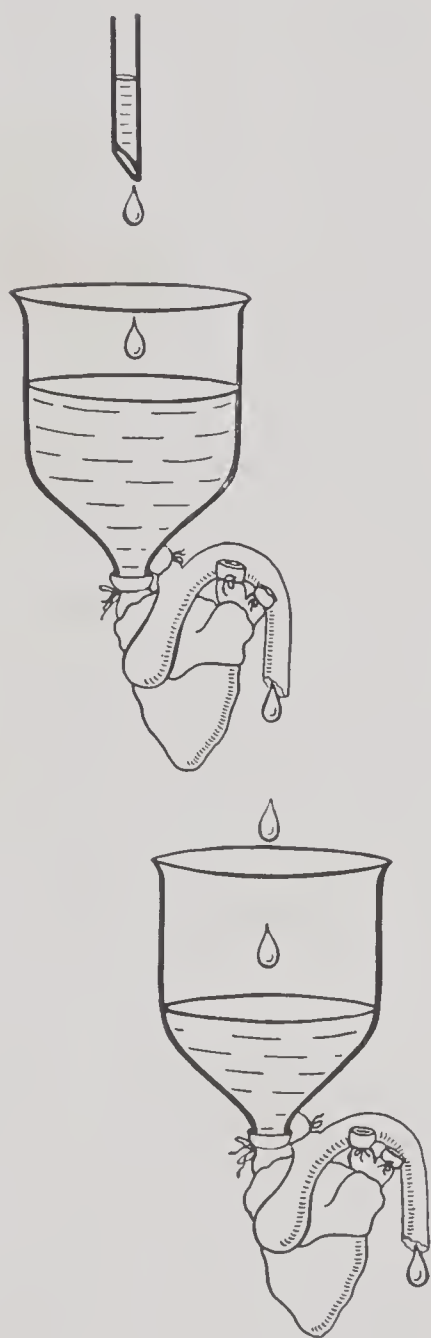


FIG. 28. The same salt solution passes through the upper heart and then through the lower one but they are otherwise entirely unconnected. Yet when the vagus nerve to the first heart is stimulated both hearts stop their beating. (Drawn by P. McC.)

the heart, discovered over a century ago, was the first case recognized, of the many now known, in which stimulating a nerve inhibited something rather than excited it. The inhibition, however, is only incidental to the present point; for the vagus stimulates other organs (it increases contractions of the gut, for example) and what is learned about its action on the heart applies equally in the other cases. When the vagus, left attached to the isolated heart, is stimulated, the heart stops. The nerve impulse has acted (somewhat indirectly) upon the cardiac muscle to keep it relaxed. This is all in order and could be accounted for satisfactorily enough even if it is the nerve action potential which stimulates the muscle. But the next observation makes such an interpretation quite impossible.

When salt solution is passed through one heart and then placed in a second one, in no way connected with the first, stimulation of the vagus nerve to the first heart stops both. If the fluid from the inhibited first heart is allowed to stand before passing through the second, the latter no longer stops. Clearly, activity of the vagus nerve

caused a liberation of some substance which is able to inhibit the heart beat. Further research soon succeeded in isolating this

substance. It is a fairly simple nitrogen-containing molecule, called acetylcholine; and there is no doubt that this nerve-produced substance, or neurohumor, is able accurately to reproduce the effects of vagus stimulation. It stops the heart, contracts the gut, and does all the other things that the vagus nerve does. Here, then, is a chemical transmitter which carries over excitation (or inhibition) from the nerve to the effector.

Clearly, if the accelerator nerves speed up the heart similarly, by liberating a chemical, it must be a different one from acetylcholine, which always stops the beat. Such a substance was looked for and found, first in connection with the action of nerves on smooth muscles, but soon for the heart also. It has been called "sympathin" because the nerves which liberate it are all members of a particular group known as orthosympathetic nerves, of which more soon. Transmission from nerves to effectors, glands as well as muscle, in the viscera thus certainly involves the liberation of neurohumoral substances at the junctions. Such substances, especially acetylcholine, are probably also important transmitters, though perhaps not the exclusive ones, between nerves and skeletal muscle and between neurones in the visceral nervous system. Possibly they contribute to transmission across synapses in the central nervous system and between receptors and sensory fibers; but it is far from proved in the latter cases and, even if chemicals play a role in these, electrical and other mechanisms are almost certainly used as well.

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CHAPTER III

STIMULUS AND SENSATION

STIMULUS AND RESPONSE. We have spoken glibly of stimuli exciting nerve or muscle and shall say more of this for sense organs. But just what is meant by a "stimulus" and by a "response"? Almost any simple definition is worthless, and a competent biologist can pick serious flaws with the ones generally current. Oddly, simple concepts, like emotions, must often grow on one gradually and then, although clearly enough grasped, are still difficultly expounded.

What is a response? A response, for example, is a change in the state of a cell or cell group, like the twitch of a muscle; but death is also a change of state and certainly not within the usual meaning of the word response. If we limit the term to a reversible change of state, we should still be including the passively stretched muscle as a responding one, for its length is reversibly altered. If we narrow the definition even further and say, "a reversible change in physiological state," this would still include as a response the greater oxygen consumption of a warm muscle than of a cool one. In a certain use of the word, this is now acceptable, for a biologist might say, "a muscle responds to warming by increasing its respiration." Yet this fails to carry the meaning we wish: a sudden discontinuous change from a resting to an active state and, further, an active state which is somehow unique to the particular cell and related to the discharge of its special function. I could go on tearing these words apart, but perhaps you begin to have some notion of what "response" implies; a nerve responds by transmitting an impulse, a muscle by contracting, a gland by secreting.

What is a stimulus? But responds to what? You say, "To a stimulus." I ask, "What is a stimulus?" and if you answer,

“Something which produces a response,” you have got nowhere—and are wrong even so. Lots of stimuli do not produce responses, because they are too weak or too brief to set into action the tissue to which they are applied. We speak of them as subthreshold stimuli, and so recognize the fact that some minimal amount of energy, or action, must be applied to a tissue before it gives its characteristic response. Well, then, can we call whatever is done to a cell a stimulus, and further subdivide stimuli into ineffective ones, which are subthreshold, and effective ones, which are threshold or suprathreshold? A stimulus is, in fact, often defined as any change in the environment of the object being stimulated, a cell or a whole organism.

Yet there are still difficulties, for often the environment continues to elicit responses while it remains constant. Nerve impulses run up the optic nerve during the whole time that a steady light is shining in the eyes. Nerve impulses continue to come from that part of the ear which helps tell us how our body is placed with respect to gravity, whether we are changing our position or not. Even skeletal muscle, kept in a solution containing certain salts, will continue to twitch at regular intervals, rather like a beating heart, so long as these salts are present. Still it is true that a change in light or position or applied chemicals is far more effective in producing responses than is the steady condition. Note that I said “change,” not “increase.” Turning out a light is just as definite a stimulus as is turning it on. A nerve gives one response when an electric current starts to pass through it, and another when the current stops; and only when the current is made much stronger does it continue to conduct impulses while the current is flowing steadily.

Mechanism of excitation. Despite the seeming ambiguity about stimulus and excitation, much detail is known about them and the manner in which certain ones work is well understood. With the aid of theoretical mathematical equations, for example, the action of all sorts of currents in stimulating nerve can be correctly and quantitatively predicted. The essence of electrical stimulation is that enough current must flow to move

the ions needed to depolarize the membrane. Let us assume the simplest case, that some fixed number of ions is necessary. Then a subthreshold current simply does not move enough of them to excite successfully.

Suppose, next, that we applied a brief electric shock which moved nearly, but not quite, enough ions to stimulate the nerve. Then, if this shock were followed by another like it, which moves additional ions, the two together should sum their effects and produce a response. And so they do, if sufficiently close together. But of course the ions do not remain where they are left by a brief current or shock; they soon diffuse back to their original positions. Consequently, the partial excitation resulting from the first shock soon dissipates itself; and the second one, if delivered after this, starts again at scratch and will likewise fail to produce a response.

Or, again, a very strong current, which moves many ions in a short time, need flow for but a brief interval to move the required number; while a weak current will have to flow for a longer time if it is to produce the response. In fact, when the current is weak enough, the ions diffuse back to their original positions as fast as the current piles them up and it never does stimulate. It is for this reason that a current which fails to stimulate almost immediately after it starts will not do so while it continues to flow steadily.

What we have learned for the electrical stimulation of nerve applies practically in toto to the normal stimulation of our sense organs. We can see an extremely bright flash of light, such as lightning, though it lasts, perhaps, only a millionth of a second. A dim flash of this duration would simply fail to register; but if it lasted longer, or were followed rapidly by a second, we would again see a single flash. When we jump into a swimming pool the water feels cold only at first. Soon we are unaware of its temperature, but then the air feels warm when we climb out. Carry a pack on your back, and you soon cease to feel the load; but later, when you take it off, you feel a delicious lightness for a short time.

You can supply additional examples from your own experience with your various senses.

The role of sense organs. A nerve fiber, we have seen, can be stimulated by almost anything. What, then, is the point of having a whole battery of special sense organs which are stimulated by the same things? They must be of considerable use, for, though the tide of evolution leaves behind some useless body flotsam, we can be quite certain that these special structures would never have appeared and evolved to their highly elaborate condition by accident. Surely it is valuable to an animal to be aware of its surroundings. The more kinds of happenings it is sensitive to, and the more sensitive it is to them, the more likely is it to make an appropriate and prompt response. It may suffice for the amoeba to detect vaguely when it is in bright sunlight and so to crawl into the shadow; but if a monkey could see no better than that, it could hardly swing its way through the tree-tops. If the deer can see or hear or smell the wolf before the wolf sees, hears, or smells the deer, it has much more chance of living out its life and raising its young. But the wolf, of course, may go hungry unless he finds other prey with less acute senses.

What all this amounts to is that the sense organs, the receptors, have been specialized so that each is far more sensitive to some one or few kinds of stimuli than is the nerve itself. It takes a tremendously powerful light to stimulate a nerve, an unbelievably weak one to stimulate an eye, when dark-adapted after thirty minutes away from light. The amount of ammonia that can be smelled or acid that can be tasted would have no effect on a nerve, although much stronger concentrations would stimulate it. And the light touch which a finger so readily detects is far from the crack on the funny-bone which excites the nerve itself. Each receptor, in other words, has a greatly lowered threshold for a certain kind of stimulus; and each one, therefore, presents a special problem in the mechanism which achieves this. But before we look into these problems we must clear up some others, about sensation in general, which we left hanging.

PROPERTIES OF SENSATION. What can you feel through your skin? Pain, pressure, temperature, touch, and other things that are probably mixtures of them, such as tickling or itching. All these we might call different qualities of sensation. But you can do much better than this, for in regard to each quality you can distinguish different intensities, a light or a heavy touch, for example, and different positions, a touch on one finger or on another. The same attributes or modalities apply to the other senses; red or blue are different qualities in vision; high and low C, different ones in hearing; skunks and roses or sweet and sour, different ones in smell or taste. But each color or tone or odor or taste may also be strong or weak and come from one direction or another. True, the direction from which a smell, or even a sound, comes can be judged with far less accuracy than can the direction of a light; but some ability remains even with smell, or "follow your nose" would have even less meaning than it does.

The problem of quality. Obviously a touch on one finger sets up impulses in different nerves from those affected by a touch on another finger; and light coming from the left reaches a different part of the retina in the eye, as of the plate in a camera, from that reached by light coming from the right. Our ability to locate a stimulus depends, then, upon which nerve fibers are stimulated by it. The quality of the sensation, whether touch or hearing, red or green, pain or cold, we have seen, also depends on which nerve fibers are stimulated, or at least on the part of the brain to which they carry their messages. But the problem of how these different nerve fibers are stimulated by the different agents is not so simple as whether nerves come from one or another finger.

The same bit of skin can give sensations of touch or cold, depending upon how it is stimulated. If impulses are set up in different nerve fibers by contact and by temperature, then each fiber must be attached to its appropriate receptor. That is, a fiber which carries impulses that give rise to a sensation of touch on reaching the brain must be attached in the skin to a receptor which has a low threshold for touch but not for cold.

If a temperature receptor happened to be connected with the "touch" nerve fiber, we should feel cold as touch, and touch would not be felt at all. It is probably just such a partial confusion, of the wrong kinds of receptors on nerve fibers, in a region of skin whose nerve has been cut and has regenerated, that leads to some of the peculiar sensations which follow this accident. It is also probable that a like confusion of receptors for red color and for green color produces some kinds of color blindness.

Actually the presence of various types of special receptors, in the skin for example, is easily demonstrated. By direct examination under the microscope, one can see strikingly different sensory endings in different positions. If those in the outermost layer of the skin are removed, by a careful slice with a sharp razor, it becomes impossible to feel touch while pain remains, more sensitive than before. Even without this mild self-mutilation you can easily show on yourself that different spots on the skin are sensitive to different stimuli. Mark out in ink an inch square on the skin of your forearm, and then carefully explore this area with the tip of a fairly stiff hair, the point of a sharp needle, and the blunt end of a metal stylus kept either ice cold or hot but not burning. Mark each point from which you obtain a sensation of touch, pain, cold, or heat, as the case may be. You will find each quality at a different spot; and you can, in fact, count in this way the number of each kind of receptor in that piece of skin.

The problem of intensity. We must still account for our ability to distinguish different intensities of any given sensation. This is the problem you faced after you were convinced that the size of the nerve impulse is independent of the strength of the stimulus that started it. If you have not yet thought about this, do so before reading on, for, with even a little proficiency in thinking physiologically, you should reach part of the right answer.

If the sensory nerve from a bit of skin is loosened from the surrounding tissue and laid upon electrodes, with care to avoid injury, we can, so to speak, tap the sensory messages on

their way from skin to brain by recording their action potentials. The first experiment shows clearly that a stronger touch to the skin produces a bigger electrical change in the nerve

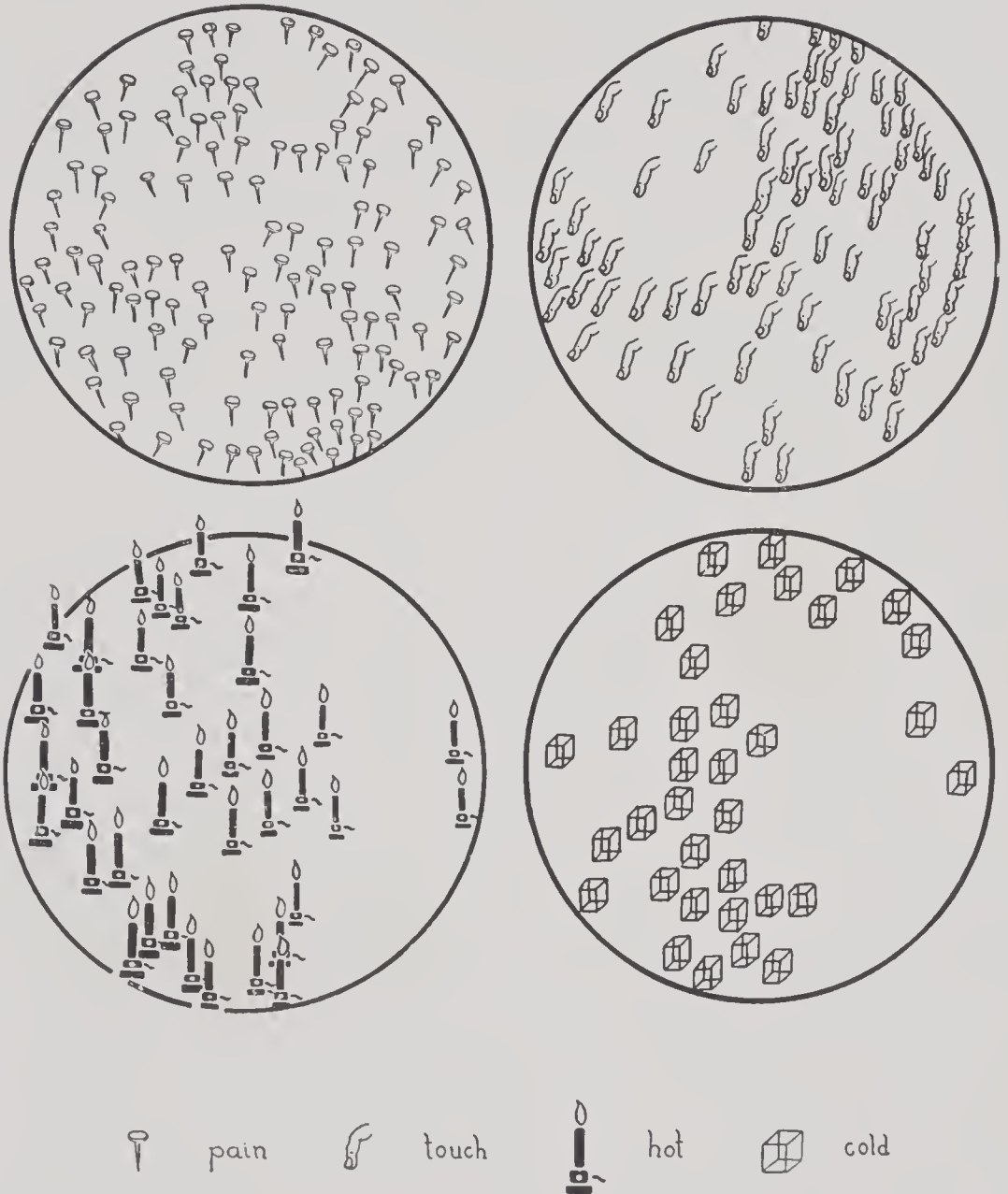


FIG. 29. A given small skin area has been thoroughly explored for spots sensitive to pain, touch, heat, or cold. The various sensitive spots were located as shown in the four circles, all representing the one skin area. Since spots for the different kinds of sensation are not all in like positions or in like number, it follows that different receptors are needed to detect the different kinds of stimuli. (Drawn by P. McC.)

bundle. Since the single nerve impulse (and its action potential) carried in one fiber is independent of stimulus strength, this can mean only either or both of two things: One, more

nerve fibers are carrying impulses after a strong stimulus or, two, each fiber is carrying more impulses. Actually, both occur. The demonstration of a change in the number of fibers active is simple enough; but to prove a change with stimulus intensity in the number of impulses per fiber—actually a more rapid succession of impulses so that, instead of coming at regular intervals of about one-fifth of a second, they tread on each other's heels at intervals of 0.005 second or less—is not so easy.

If the impulses in all the fibers of a bundle were in perfect time with each other, a great electrical wave would pass with each discharge, and these waves could be timed and counted. But this is not the case. Impulses travel at different speeds in different fibers, and start at slightly different times, so that the electrical changes in the whole bundle are going every which way at once; like a poorly trained chorus whose members are singing out of time. The solution is obvious enough in theory, but you now have some idea of the difficulties of putting it into practice: simply cut all the nerve fibers but one, and measure the action potentials from it! Well, it has been done, by dissecting under a microscope and by using electrical apparatus able to amplify the minute potentials many million times. (Some more Nobel prizes were awarded for such achievements.)

When a touch or other receptor is subjected to a steady stimulus, the impulses running up its nerve fiber come at a high frequency; and the stronger the touch, the more closely do they follow one another. But, although the stimulus is held unchanged, the frequency rapidly falls off; the receptor, we say, adapts. This is why you are practically unaware of your

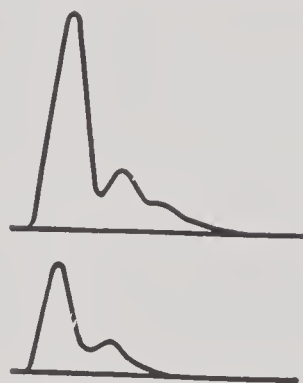


FIG. 30. Diagrams of action potentials in a sensory nerve, set up by a weak stimulus (below) or a strong one (above). The diagram illustrates the increase in height with a stronger stimulus, as discussed in the text. Note also the additional point, not mentioned, that some of the extra fibers activated by the strong stimulus develop action potentials which follow after the main ones and appear as the small waves shown to the right. (Drawn by P. McC.)

clothing while it is making a constant pressure on the skin, but rediscover it when some movement changes this pressure. In the same way, a burst of closely grouped impulses travels along the optic nerve when a light is turned on, the frequency varying with the brightness; while the light shines impulses get fewer and fewer; and a fresh burst appears when the light is turned off (Fig. 31). The receptor is able to control the frequency of impulses set up because a stronger excitation from it will cause the nerve to respond earlier in its refractory



FIG. 31. These actual records of action potentials from the optic nerve show a large burst of nerve impulses when light is turned on (indicated by blacking out of the white line below) and another burst when the light is turned off. Relatively few impulses travel during steady illumination. (Courtesy of H. K. Hartline.)

period; but perhaps you had better not worry about the details.*

How a stronger touch to a given skin area starts impulses from more touch receptors, however, we can understand easily.

* The control of muscle contractions by the central nervous system is the motor counterpart of the behavior of the sensory system. Which muscle contracts depends on which of the motor neurones discharge impulses along their axones, and this depends in turn on what nervous or chemical stimuli are acting upon their dendrites and cell bodies. How strongly and for how long the muscle contracts are controlled by the number of motor units called into action and by the frequency of the impulses to each group of muscle fibers. The neurone, like the receptor, discharges impulses at a higher frequency and for a longer time when more strongly stimulated; and a more rapid series of nerve impulses gives a stronger tetanic contraction of the muscle.

This again is easily tested on yourself, for you can actually hear the contraction of some jaw muscles which pass your ear! Put a pillow over each ear, to intensify internal sounds and decrease external ones, and then clamp your closed jaw with various strengths of contraction. You will hear a clear rumbling in both ears, louder and more high pitched as the teeth are pressed together more tightly. Now, instead of clamping it, move your jaw to one side, farther and farther. You will hear the muscles on that side of the head contracting and, if you experiment a bit with feeble movements, you should be able to hear and count a series of regular ticks, several a second, which tell you exactly how the nerve impulses are tetanizing some particular group of muscle fibers. Try this in bed some night or morning.

The different individual receptors must vary somewhat in their threshold. Those covered by a thinner layer of epidermis or lying at the base of a fine hair, for example, would be set off by a very light touch; those less fortunately situated or intrinsically less sensitive would be brought in by stronger touch. The same principle applies to the eye and to other sense organs, although in these any difference in location of the receptors is less important than are differences in their native sensitivity.

THE SENSES. So much for mechanisms; now just what receptors have we, and how many senses? The proverbial five senses—vision, hearing, smell, taste, and skin or cutaneous sensation—are a small part of the lot. They are, to be sure, the main ones which give us information of the outside world, but note that the lot of them leaves us quite insensitive to many changes which are continually occurring. We cannot sense X-rays or cosmic rays, infra-red or ultra-violet, radio waves, sounds of too high or low a pitch, or magnetic fields; and, oddly enough, electrical currents, to which nerves are so exquisitely sensitive, are detected only as they act directly upon nerves, for there are no special receptors for them.

Distance receptors. Our sense organs have evolved slowly and are a remarkable achievement. Relative to the eye of a snail, our own is like a high-grade camera with sensitive color film compared to a box with a pinhole and containing cheap bromide paper—it is sensitive to far smaller amounts of light and to a much wider spectrum, it responds far more rapidly, and it distinguishes colors and patterns. In man's evolution, first the nose and later the eyes and ears were the important distance receptors, for they brought information about things happening far from the animal. If you can smell or hear or see your enemy (or your food) at a distance you are less likely to feel his claws and teeth on your tender anatomy. But animate objects, important in an animal's world, produce only tiny electrical currents which do not leave the body, they give off no X-rays or magnetic fields; so that, had animals

developed receptors for these, they would have been useless under the natural conditions of existence. For similar reasons we have eyelids; an animal well holed up can afford to sleep even in daytime, and it is useful to exclude the sunlight. But sounds are made by movements, always potentially dangerous, so there are no earlids to close in sleep—though civilized man, living in the security but hurly-burly of modern cities, often wishes he had them.

Visceral sensation. Those sense organs on the surface of the body which tell us about the outside are collectively known as exteroceptors. We also get plenty of conscious information from inside our body, however, and the sense organs involved in this are called interoceptors. There is a great variety of these, giving rise to many qualitatively different sensations: thirst, largely from the throat when it becomes dry; hunger, from contractions of the stomach, changed by still other movements to nausea; the need to defecate is felt when the rectum is distended, to urinate when the bladder is filled; pain is produced by stretching or inflammation of almost any viscus, colic similarly by contraction; and all sorts of other sensations, less clearly recognizable as definite entities—as heartburn, palpitation, fullness, warmth, etc.—are thrown in for good measure. But those few impulses, from interoceptors, which ultimately find their way to the brain and to consciousness are an insignificant fraction of the many constantly set up during the normal working of the visceral machinery, and of which we remain serenely unaware. Every second, afferent impulses are arising in heart, blood vessels, lungs, gut, and so on, which are of the utmost importance in controlling the activity of these organs, as we shall see in the next chapter, but with which our conscious attention is completely unconcerned.

Position and movement sense. Do you think, now, that you have in mind all the senses you possess? Very well, shut your eyes, extend your right index finger at some convenient position in front of you, and, eyes still closed, touch its tip with your left index finger. Too easy? Then have a friend move your right arm and finger into some position behind your back,

and again touch it with your left finger. Still easy? Yes, perfectly simple and automatic for a normal person; yet think of what it involves. How do you know, without seeing it and when someone else has placed it, just where in space the finger tip is? How are you able to control the contractions of dozens of muscles, which move the shoulder, elbow, wrist, and finger joints, so that the seeking finger tip moves smoothly through space and exactly to its goal? Some sort of information from the muscles, the tendons, and the joints must continually be reaching your brain, even though you are not very aware of it, which tells you just how much they are contracted or stretched or bent and, therefore, the position of the arm relative to the body.

When your leg has gone to sleep that "dead" feeling in it results from the absence of such sensations; and if someone moves your leg about when it is in this condition, while you try, with eyes shut, to touch your big toe, you will realize how all-important such sensations are. In several diseases of the nervous system these proprioceptive sensations, as they are called, are interfered with or lost. Persons suffering from such diseases are often unable to maintain themselves erect, except as their eyes warn them when they start to sway in one direction or another; with eyes closed they topple over. You may have seen old men walking along the street, with the aid of a cane, awkwardly slapping their feet ahead of them step after step, leaning over and constantly watching like hawks to guide themselves in even these crude movements. Proprioceptive receptors are probably more numerous and more continuously active than any others, although they claim the least attention of all.

There are still other closely related receptors, in a portion of the internal ear, which help to balance the body as a whole. They are stimulated by the pull of gravity, which acts through tiny bone-like pebbles hung from sensitive hairs, and they tell us when we are right-side-up or in some other position. It is the excessive and rapidly changing stimulation of these receptors which produces the funny feeling we experience in a

quickly rising or falling elevator, and brings on seasickness or the dizziness from whirling around rapidly.

This account is still far from exhausting the kinds of sensation which man experiences; think, for example, of those associated with the sex organs. And we are quite certain, from the different structures of receptors of many animals, that they experience still other sensations unknown to us, although of course we cannot guess at their qualities.

Sensation and affect. It may have occurred to you that, as most proprioceptive sensations are barely conscious and emotionally quite indifferent, so interoceptive ones, when they become conscious, are likely to carry a good deal of affect, or feeling, with them. They are not neutral, but definitely pleasant or, far more often, unpleasant. This is natural enough, since they are usually signals that something is wrong or needs to be done.* The skin sensations are intermediate. Pain is certainly unpleasant, as are also extreme temperature or pressure stimuli. Often *you* feel hot or cold, and uncomfortable about it; but at other times the *object* you handle feels hot, not you. Temperature sensations, therefore, may be referred to the body or to the outside. Touch is always referred outside, except in such special forms as tickling or itching. And, of course, the distance receptors bring sensations which never seem to come from within the body, but always from outside of it; even the light flashes produced by stimulating the optic part of the brain are sensed as if somewhere out in space. Further, such sensations, of themselves, have no feeling quality at all. Whatever joy or unhappiness is produced through hearing and vision depends upon our past experience and the meanings this has taught us to weave around the raw sensations.

Receptor mechanisms. A tremendous amount of knowledge has accumulated about the way in which various receptors work; about how one particular kind of stimulus leads to the discharge of those vital nerve impulses from each type of sense organ. We shall not, unfortunately, find time later to examine

* We shall learn more of feeling later.

how the eye and the ear, the skin and the muscle receptors, are excited and in turn excite their attached nerves; for all sorts of elaborate and special mechanisms are involved. The high-grade variable lens and shutter, for example, which make the eye such an excellent camera, have nothing directly to do with the sensing of light; such sensitivity depends, in the camera, only on the film, in the eye, only on the retina.

But certain aspects of stimulation are common to large numbers of receptors. Every one is stimulated by either a chemical change or a mechanical deformation. Hearing depends on waves, in the fluid of the ear, which move a floating membrane against minute hairs and stretch or bend them; so the hearing part of the ear, like that devoted to balance, is a specialized type of touch receptor, stimulated by mechanical deformation. The same is true for many of the visceral receptors, which respond to stretch or pressure. Taste and smell are the obvious chemical senses, but the temperature receptors of the skin also are probably actually excited by chemical changes induced by heat or cold. And our eye, the prize of the lot, is another chemical receptor; for light falling on the retina bleaches colored substances contained in this sheet of receptor cells and produces other photochemical effects analogous to, though of course different from, those in a silver bromide emulsion. Rather a remarkable achievement of evolution— isn't it?—to develop hearing from primitive touch, and vision from primitive taste; and to create all our senses, with the extraordinary knowledge they give us of a universe about us, from the bending of films and the interaction of molecules!

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CHAPTER IV

INTERNAL INTEGRATION

INTEGRATION. You are you, a single individual different from all others. You respond to the world about you as a unit. You have the subjective awareness of unity, of being one whole person. Even if the upper part of your brain, the great cerebral cortex which dominates your “willed” and “intelligent” actions, were gone, you would still continue to function quite well as a living machine—although hardly as a social companion—for you would continue to breathe, digest, excrete, balance yourself, move about in coordinated fashion, and the like. Yet you are composed of billions upon billions of cells, over 10 billion in the nervous system alone and 5 billion in each cubic centimeter of blood—and you possess about 5 liters of this precious fluid! This question must be answered: How does a new oneness arise out of the myriad tiny cell individualities; how are these separate units integrated together so as to become the single highly organized and efficient human body? The gist of the problem is in the word “integration,” for a mere piling up of cells, even of various kinds, would lead only to confusion. Rather, the cells must be related in patterns of structure and function of ever-increasing complexity to produce such a really amazing new individual as yourself. What, then, are the mechanisms which bring about the coordination of cells?

COORDINATING MECHANISMS

For one thing, mechanical forces are important. We have already seen how the muscles produce tension and movement of other parts of the body and are, in turn, influenced

by tensions exerted from other parts to develop their positions and structures. In the same way, bone cells line up and deposit their mineral trusses and girders accurately along lines of compression and stretch set up by the weight of the whole body. Other examples, of how various cells are shaped and arranged by the pressures of adjacent ones, and of how blood pressure acts mechanically to force fluids among cells, could be given in large numbers; and you know that mechanical factors are important in stimulating a large number of receptors. But this situation is sufficiently simple so that we can pass it by without more ado.

A second coordinating factor is the agents, mainly chemicals, transported from one place to another. This mechanism operates ever more efficiently as the means of transportation, mainly the blood stream, are improved and as the chemical messengers become more powerful and precise in their action. We shall thus have to examine the blood and the substances added to and taken from it by various organs, especially by the glands of internal secretion, if we wish to learn more about coordination through transported chemicals.

A third means of making a single organism of its many cells is transmission—the spread of excitation rather than of substances from one body region to another. Transmission does not demand the presence of nerves, for it occurs in plants and simple animals which have none. Even in your body some non-nervous control exists whereby more active cells or body parts dominate over and keep in check the performance of less active ones, so that quantitative gradients in rate and intensity of activity play an important role in integration. But when a nervous system is present, transmission does overwhelmingly depend upon the conducted nerve impulses.

THE AUTONOMIC NERVOUS SYSTEM. We have seen how a stimulus at one place, acting through receptor, nerves, reflex center, and effector, may produce a response at a far distant place. But we have given most attention to the responses of the whole organism to its surroundings. Now

we must look more carefully at that portion of the nervous system—variously called visceral, vegetative, sympathetic, or, best, autonomic (meaning self-regulating)—which is particularly concerned with the internal adjustments of the various body parts to each other.

Distribution and function. When you were a tiny embryo in your mother's womb, composed roughly of a double plate of cells, the outer layer of cells folded up upon itself to form a hollow tube which finally developed into the nervous system. The primitive neurones in this tube multiplied profusely, then sprouted their various processes to form the nerve tracts in the central nervous system and the peripheral nerve trunks which run from the central system to the rest of the body. The nerve cells themselves remained massed together in the brain and spinal cord, except for a few wanderers. These squirmed their way among other cells, some remaining as small cell groups, or ganglia, along each side of the spinal column, others continuing on to enter the various viscera as these formed; but all the neurones remained connected, through their cell processes, with the parent nervous system. These scattered, yet connected, neurones constitute the autonomic nervous system which innervates practically all the organs of the body.

The great duty of this system is to regulate the activity of these organs from moment to moment, so that they respond accurately to the changing needs of the organism. When food is eaten, the digestive system must become more active; when muscles are exercising, the heart must pump more blood to them and the lungs must bring more oxygen into that blood; when the urinary bladder is full, it must contract and expel its contents. Such timely actions are largely under the control of the autonomic nerves.

The ortho- and parasympathetic divisions. Now, if you wished to arrange for the accurate control of something, say the speed of an automobile or the placing of an object, would you have just one means of maneuvering it or two opposed ones? Think, for example, of how you guide a chisel; do you not

use one hand to push and the other to restrain the tool, so that if the wood suddenly gives or the point turns off its course you can stop it promptly? When you have partially built a house of cards and are placing the roof, you achieve the delicate movement by steadying one hand with the other. In fact, even in ordinary movements, your skeletal muscles carefully balance one another so that, when the flexors, for example, contract, the extensors which oppose them relax. And of course the automobile speed is controlled not only by the gasoline feed pedal which accelerates it but also by the brake pedal which slows it down. Free-wheeling is not a success, despite its many advantages, because the engine cannot be used to help brake the car. Well, nature misses few bets, and the autonomic nervous system also makes use of the principle of opposed forces to grade visceral performance finely.

Each organ or tissue receives two sets of autonomic nerves (and, except for skeletal muscle, no other kind) which act upon it in opposite directions. The heart is speeded up by the accelerator nerves and slowed by the vagus, and so on down the line. There are, correspondingly, two subdivisions of the autonomic nervous system, known as the orthosympathetic and the parasympathetic. (The whole autonomic system is often called the sympathetic system and the two divisions are thus labeled as the straight or direct one, "ortho-," and that opposite or opposed to it, "para-." These two divisions are distinguished anatomically, for it is the orthosympathetic cells which remain close to the backbone and send their long axones on to innervate the viscera, whereas the parasympathetic cells go all the way to the tissues where their cell bodies form ganglia or plexuses right in the substance of each viscus they innervate. Further, the two systems are chemically different; sympathin is liberated at the endings of orthosympathetic fibers, acetylcholine at the endings of parasympathetic ones; and various drugs which are able to stimulate or depress one system may be quite inactive on the other. And of course the two systems differ in their functions; for, when the nerves of one stimulate any particular viscus, those of the other inhibit it.

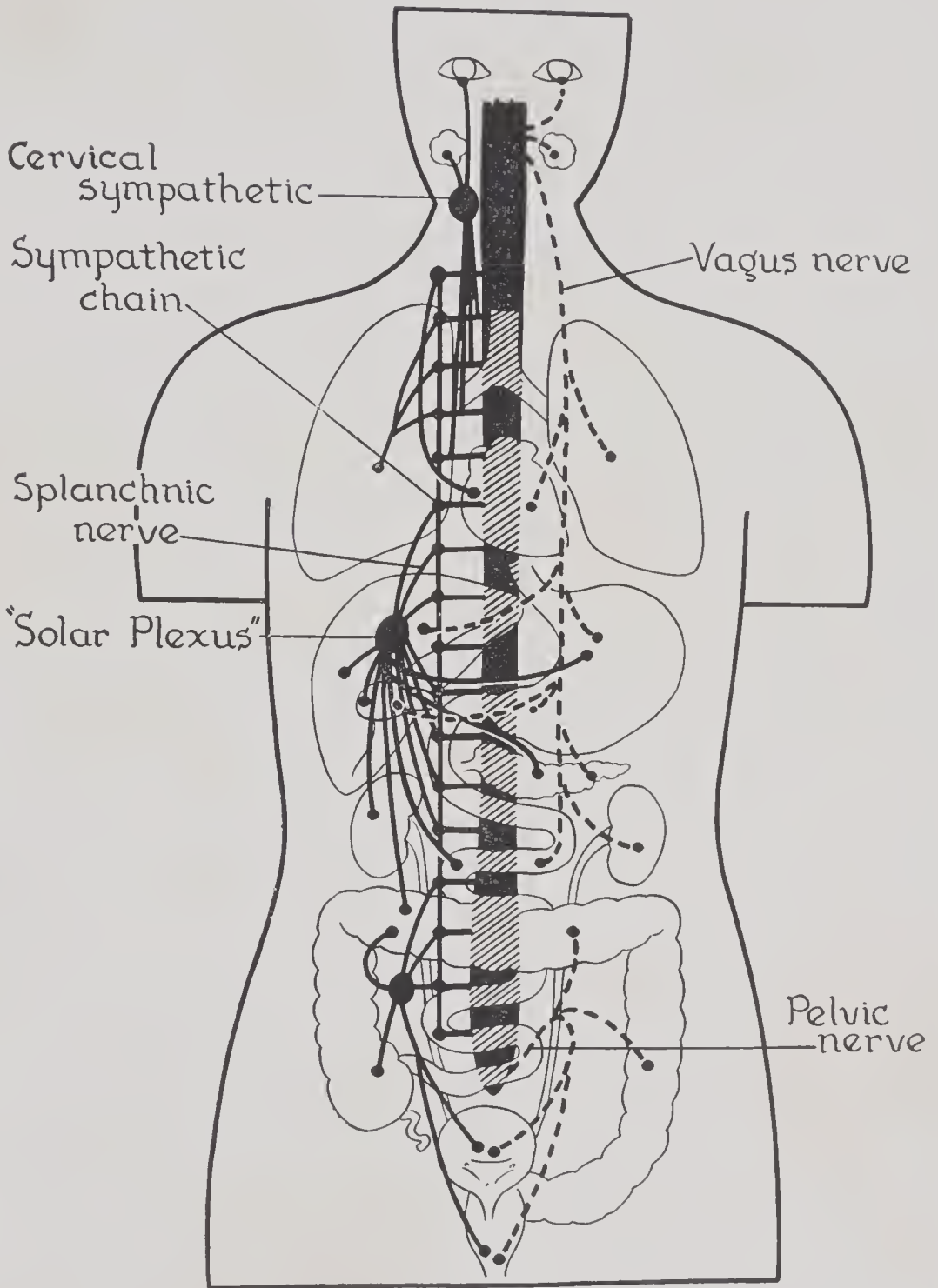


FIG. 32. The nerves shown coming from the nervous system to the right side of the figure are the parasympathetic nerves; those to the left, the orthosympathetic ones. Note that the former come from the upper (cranial) and lower (sacral) regions, the latter from the midportion (thoracic and lumbar) of the spinal cord. The parasympathetic nerves pass directly from the central nervous system to the various organs, with no synapses before reaching ganglia in or very close to the organ itself. Orthosympathetic nerves enter ganglia, mainly in chains near the spinal column, and synapse at a distance from the organs they supply. Remember that the two systems act oppositely on any one viscus. (Drawn by E. M.)

The action of autonomic nerves. At this point we meet a peculiar irregularity for which there exists as yet no adequate explanation. Neither the ortho- nor the parasympathetic system is always excitatory or inhibitory; their effects differ in the various viscera. Thus the orthosympathetic nerves speed up the heart; constrict the blood vessels; contract those circular bands of muscle, the sphincters, which, by shutting down or relaxing, control the openings of the urinary bladder, rectum, stomach, gall bladder, and other passages; erect the hairs; and cause secretion of the adrenal and some other glands. The parasympathetic nerves stop or decrease all these actions. On the other hand, it is the parasympathetic nerves which cause contraction of the stomach and intestines, of the urinary and gall bladders, and of the pupil of the eye, and lead to secretion of the salivary and other digestive glands, the sweat glands of the skin (these and the hairs are somewhat atypical cases). The orthosympathetic nerves act as the inhibitors of all these.

If we know the action of each division on various effectors, it is simple to understand the effects produced when one or the other is overly active, as a result of such body conditions as anger or fright or the use of certain drugs. The orthosympathetic system is stimulated by adrenalin, an internal secretion of the adrenal gland. It is also stimulated pretty generally by such emotional states as fear, pain, and rage, and, since orthosympathetic nerves to the adrenal cause it to pour adrenalin into the blood, the effects of the chemical and of these emotions are very similar. When you are thoroughly frightened your pupils become large, your hair stands on end, constriction of blood vessels makes your skin pale and your blood pressure high, your heart palpitates, movements of your intestine are stopped; in short you show all the bodily effects of a good fright. Injection of a large dose of adrenalin produces the same bodily effects but without the feeling.

An injection of atropine, on the other hand, by paralyzing the vagus and other parasympathetic nerves, leads likewise to a rapid heart, a paralyzed gut, a dry mouth, and dilated pupils. In fact, atropine is the active ingredient of belladonna,

long used by women to dilate their pupils and give a supposedly soulful look to their eyes; at least "bella donna" means "beautiful woman." Perhaps you have already tried a cigar or can remember when you first smoked a cigarette of real tobacco instead of corn silk. You were pretty sick and miserable because of the action of the nicotine you inhaled. This drug first stimulates and, in large doses, later paralyzes the autonomic ganglia; and the alarming symptoms you felt and showed under its action will give you a better idea than any words of the powerful and universal action of these nerves.

Autonomic reflexes. The autonomic system, then, gives a double efferent innervation which regulates the activity of body organs; but these efferent discharges must in turn be controlled just as are those to skeletal muscle. The mechanisms are the same. The many interoceptors in the viscera are supplied by autonomic nerve fibers which carry the afferent impulses to the ganglia, and indeed many of them carry on into the central nervous system. The neurones in one ganglion or those in separate ganglia are interconnected through their processes and synapses; thus perfectly good reflex arcs enable the autonomic nervous system to function even when the central nervous system is entirely disconnected from it or, for that matter, largely removed from the body. But the independence is not complete; else, for example, we should never become conscious of visceral sensations; nor could a horror story or a sudden fright produce a cold sweat and a palpitating heart. Both sensory and motor connections between the two nervous systems are present and function continuously; in fact, the nerve centers which control the coordinated discharges of large groups of autonomic nerves are all located within the central nervous system.

Thus, when your skin is strongly scratched with a blunt point, a red flare appears some distance to either side of the scratch because the distant blood vessels dilate under the influence of autonomic reflexes. On the other hand, the general flushing of the skin when you get too warm, and which helps cool the body by bringing more warm blood to the

surface to lose heat, is produced through autonomic nerves but is controlled from a part of the central nervous system. The traveling of a peristaltic wave along the intestine depends on local autonomic control and occurs when all outside nerves are cut; but the stomach contractions which, by producing hunger sensations, warn that it is time to refuel the body depend mainly on messages coming from the central nervous system. The solar plexus blow produces an abnormal stimulation of visceral receptors, which, by reflexes through the medulla* and parasympathetic nerves, slow the heart and dilate the blood vessels, so that insufficient blood reaches the brain and unconsciousness results. Normally, special receptors in the walls of the heart, the aorta, and the large arteries to the head produce a similar reflex fall in blood pressure; but, since they are stimulated only when these vessels are stretched by high blood pressure, and the stimulation automatically stops as soon as the pressure is lowered, no fainting results but only a neat control which keeps blood pressure very constant.

Such autonomic reflexes are fragments of the more widespread and coordinated actions which this system brings about, but even these fragments show how intimately all sorts of organs and mechanisms interact.

CHEMICAL REGULATORS. Before sketching these larger patterns, therefore, we must return to the transportative mechanisms and learn more of the action of the chemicals and of the transporting medium.

Carbon dioxide. Consider a cell, say a muscle cell, and the problem of supplying it with oxygen. Blood flows through capillaries in its neighborhood and oxygen diffuses from the blood to the muscle. The resting cell requires a certain amount of this gas each second to maintain its metabolism; but the

* The medulla is that part of the central nervous system, at the top of the spinal cord, which contains many important reflex centers for controlling circulation, respiration, and other functions. You might as well now get acquainted also with a still higher part of the central nervous system, the hypothalamus, which in many respects acts as the main coordination center for all visceral activity. (See Fig. 86.)

blood passing in the same time interval carries rather more oxygen than is needed, so that some sweeps by into the vein, and the muscle is well cared for. Now the muscle cell and its neighbors contract vigorously; their metabolism is multiplied many times, and the oxygen required is far greater than that being supplied by the blood. To be sure, the lactic acid mechanism, which permits an oxygen debt, will help tide them over for a while; but ultimately this debt must be paid, and the sooner the better, so that a greatly increased supply of oxygen to this muscle cell must be achieved. The most obvious, direct, and efficient method would be to increase the amount of blood flowing past the muscle each second, and this would result from a dilatation of the blood vessels in its vicinity.

Here, then, is the problem: How are the muscle cells in the contracting skeletal muscle to "inform" the smooth muscle cells which control the caliber of the nearby fine arterioles that the latter should relax and let more blood through? Well, how would you manage it? Would you build a reflex from skeletal muscle to autonomic ganglion and back to smooth muscle, so that receptors in the skeletal muscle are stimulated by its contraction and lead to inhibition of the muscles in the blood-vessel wall? It might work, but what a cumbersome thing it would be; for a separate reflex arc would be needed between practically every single muscle fiber and its local blood vessels. It would be as inefficient as communicating with someone in the next room through the city-telephone exchange.

How much simpler to use a chemical mechanism in which some substance formed by the muscle acts directly upon the blood vessels. Ideally, such a substance should be a constant product of muscle metabolism, it should increase in quantity in proportion to the muscle's activity and oxygen need, and it should normally diffuse from the muscle to the blood stream to be carried away, for then a change in its concentration would automatically control the caliber of the vessels it reached on its way to the blood. Does this strike you as a difficult set of conditions to fulfill; or have you already the answer? A

cell produces carbon dioxide steadily and in proportion to the oxygen used; the greater the metabolism, the more carbon dioxide produced. The carbon dioxide diffuses from muscle to blood, to be carried on in a manner analogous to the movement of oxygen. The problem would be solved perfectly if carbon dioxide were able to dilate blood vessels. Now it is a fact that the blood vessels to muscle dilate greatly when the muscle becomes active, and will still do so even when all the nerve connections have been cut. This certainly makes it likely that some chemical mechanism is controlling them, but doesn't prove that carbon dioxide is the agent.

If you have a chance, examine the blood flow through the thin and nearly transparent web which connects a frog's toes (nothing but a frog and a microscope is required). You will see a beautiful and exciting moving picture of the blood rushing through thousands of tiny tubes which branch and rejoin in a bewildering pattern. You can easily produce carbon dioxide by dropping acid on some chalk in a bottle. Can you carry on the experiment to prove for yourself that this substance actually can dilate blood vessels?

Suppose, next, that not one but many muscle cells become active and that great numbers of blood vessels through the body dilate. This might so far lower blood pressure that all the cells, instead of receiving more blood, actually would receive less. Before worrying about this let us consider the next limit set upon this mechanism. The blood is moving through the body more rapidly than before and giving oxygen to the muscles in much greater quantities. But the blood has no significant store of oxygen in it; it must be restocked in the lungs as steadily as it is depleted in the tissues. To be sure, if the blood is circulating more rapidly, it can pick up more oxygen from the air-containing sacs in the lungs, just as it can give off more to the muscle; but then the air and its constituent oxygen must also be supplied to the lungs more rapidly than before, and respiration must be increased. That this happens is obvious enough—run rapidly up a few flights of stairs and note the change in rate and depth of your breathing—but

the question remains: What is the mechanism which increases respiration enough to supply the extra oxygen requirement? Carbon dioxide would again be a reasonable and a correct guess. Increased concentration of this substance in the blood going to the medulla, which controls the nerves that move the



FIG. 33a. Photomicrograph of capillaries, showing red blood cells passing through singly or in groups. (From the film, *The Circulation of the Blood*, by Carlson.)

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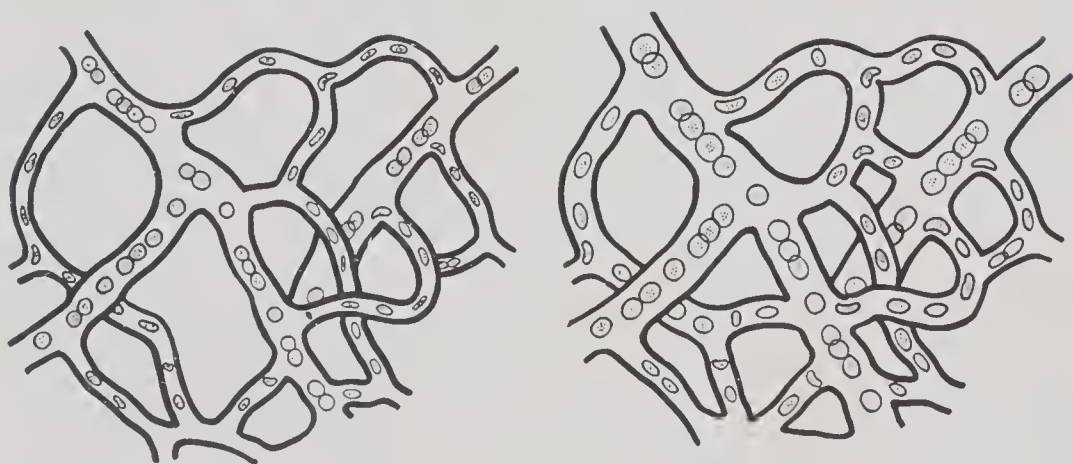


FIG. 33b. The diagram on the left illustrates the capillaries as seen in the web of a frog's foot under ordinary conditions; that on the right shows the same region of capillaries when acted upon by carbon dioxide. Note that when the vessels dilate some additional ones, which were so constricted as to be invisible, appear as if from nowhere. (Drawn by P. McC.)

chest and diaphragm in respiration, stimulates it to greater activity, and thus increases respiration. You can surely devise some simple experiment to prove on yourself that an increase in carbon dioxide augments respiration.

Now note the position we have reached. A particular substance formed by certain cells moves, by diffusion or cir-

ulation, to reach other different cells and to alter their activity. The smooth muscle cells of blood vessels are inhibited by this substance, the neurones of the medulla are stimulated, and, in both cases, the changed activity brings about results which are adaptive; that is, useful to the whole organism and to the original cells. Carbon dioxide serves as a chemical messenger, produced by one cell, transported, and producing physiological changes in others. But this statement is a pretty good definition of a hormone; and carbon dioxide should perhaps be regarded as one of the most primitive of these substances. It is certainly not specific in origin, for all cells produce it, or in action, for it influences the behavior of many more cells than have been indicated; and it is mainly in a greater specificity, particularly of production, that the substances more orthodoxly called hormones differ from it. But this is only a matter of degree and definition, not of kind.

Secretin. The word, hormone, means a substance which stimulates. It was coined at the beginning of this century to characterize secretin, the first of these substances clearly identified. The pancreas is in part a digestive gland, pouring powerful juices through its duct into the upper small intestine. (See Fig. 66.) There it mixes with foodstuffs and its enzymes help digest all the important ones. It would certainly be inefficient were this large gland continuously to squander its valuable products on an empty intestine; in fact it could even be dangerous, for the juice might digest the proteins of the intestinal cells themselves. The food we eat at a meal remains for several hours in the stomach, where it is mixed with the strongly acid gastric juice and its digestion is begun. The pancreas does not secrete during this time in any significant amount, but, when the stomach's sphincter relaxes and its acid contents begin to squirt into the upper intestine, the pancreas promptly goes into action.

Experiments soon showed that whenever an acid was introduced into the intestine the pancreas began to secrete. It was difficult surgically to destroy the nerve connections between the intimately joined intestine and pancreas, but this was

finally achieved; it did not prevent the response of the gland. Clearly then, some substance passed from the intestine to the pancreas and stimulated the gland to secrete its juice. Perhaps the acid itself? No, because acid introduced into the blood through other routes than the intestine (actually other routes than the upper part of the intestine, the duodenum) had no such effect. The acid, then, must liberate in the wall of the duodenum some substance which enters the blood stream to reach the pancreas. A particularly convincing experiment, to prove the existence of such a substance in the blood, is to

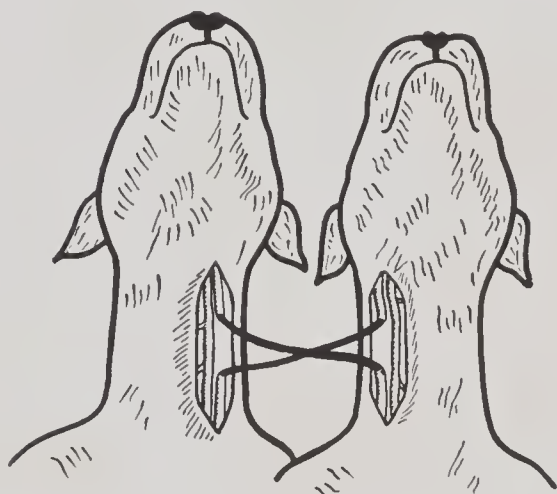


FIG. 34. By connecting the neck arteries (carotids) of two dogs with rubber tubing, as shown, all the blood is made to flow through both animals alike in the course of its travels. Such a "cross-circulation" experiment is especially useful in demonstrating control of body activity by a chemical circulating in the blood stream. (Drawn by P. McC.)

connect the blood vessels of two dogs, so that their common blood flows through both animals. Then putting acid in the duodenum of one should make the pancreases of both secrete, and it does.

At this stage a scientist would be justified in naming the substance, even though it were not yet isolated. It was named for its demonstrated action of stimulating secretion. The next steps, of course, would be to identify the substance chemically and to learn exactly where it is formed, how liberated, etc. These studies are not yet complete, although we do know that secretin is a relatively simple protein molecule,

present in combined form in the intestine and liberated from it by acid. Extracts of the intestinal wall have been made and considerably purified, and these, on injection into the blood stream, produce an abundant flow of pancreatic juice.

Other hormones. After the discovery of this hormone there was a tremendous burst of successful activity, and each of the glands of internal secretion (the word endocrine means internally secreting) was figuratively torn apart by a host of eager experimenters. A single gland was removed and the resultant symptoms studied; extracts of a gland were made, injected into other animals, and the effects observed; particular diseases of human beings were shown to be associated with destruction or abnormality of certain of their glands (actually some of this clinical evidence was known far earlier); and chemists began to identify, and later to manufacture, the active hormones. The pituitary, also called hypophysis, the thyroids, and parathyroids, the pancreas, the adrenals, the placenta, the testes and ovaries—not to mention the less important or certain instances of pineal, thymus, liver, etc.—were soon shown to have an endocrine function. Some were found to form, not one, but several hormones, each doing its own particular job; and new hormones produced by these glands are still being discovered yearly—at least a dozen active principles are already recognized in the pituitary.

We have seen something of how adrenalin, one of the adrenal hormones, acts. This was the first to be purified, chemically analyzed, and successfully synthesized. It is a relatively small and simple molecule and so will diffuse through membranes which hold back many others. This happy circumstance made possible its isolation from the blood itself by having the blood run through tubes made of a membrane which allowed the adrenalin to diffuse through into a pure salt solution. Thyroxin, the active portion of the important thyroid hormone, contains four atoms of iodine in its molecule, which served as a handy label in its isolation. This hormone, although formed only in the thyroid, is not very specific in its action, for it increases the oxygen consumption of most cells,

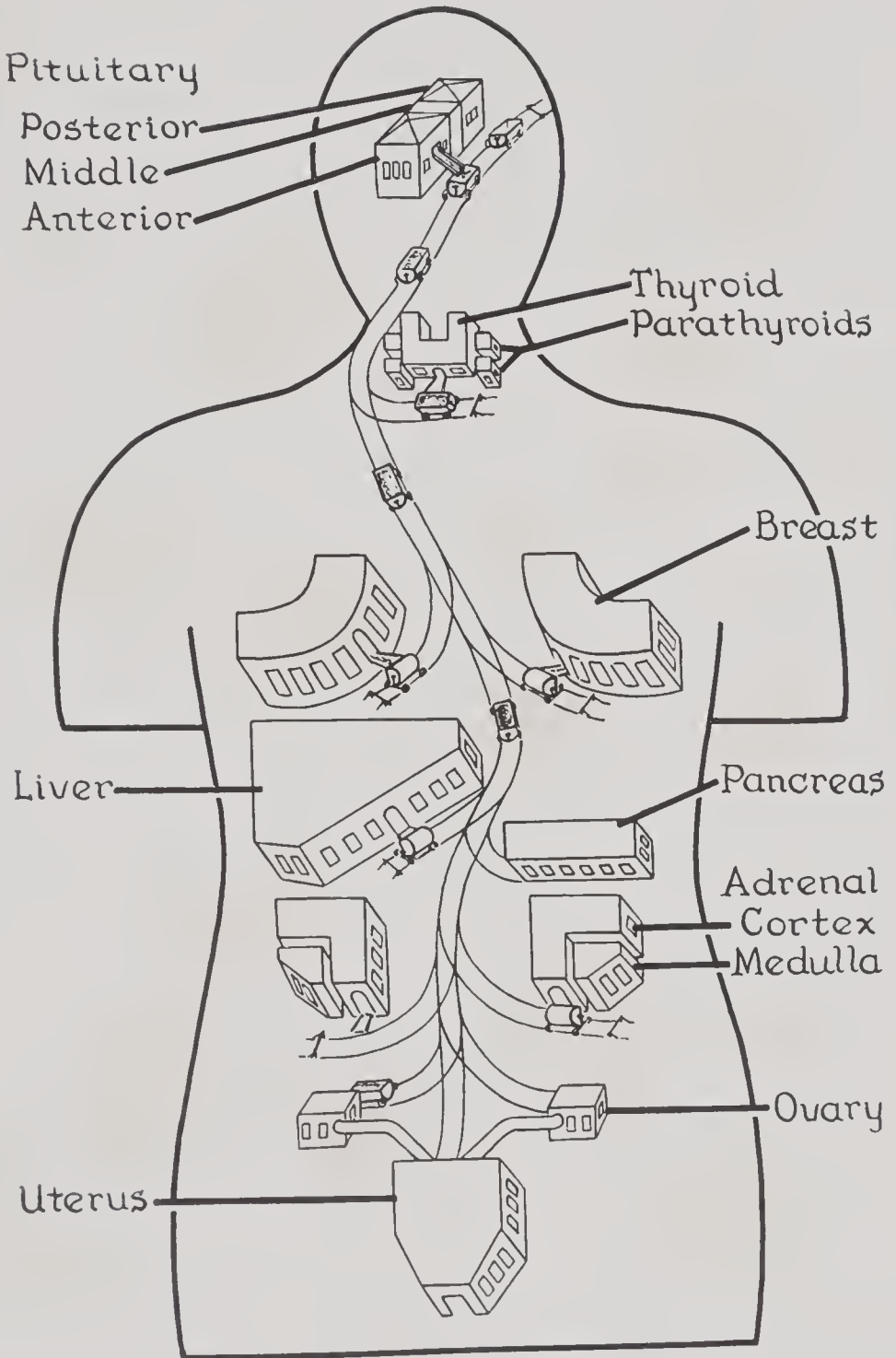


FIG. 35. Here is one way of thinking of the endocrine glands, located about the body as indicated, manufacturing their special products, and shipping them off in the blood stream. The tracks do not represent the positions of actual blood vessels.
(Drawn by E. M.)

perhaps of all. The hormone of the pancreas, insulin (so called because it is formed only by small islands of endocrine cells scattered among the greater number of cells which secrete digestive juice), is necessary to the proper metabolism of sugar by the body. In its absence fatal diabetes results.

The various endocrine glands act not only on other organs but also on each other. In the absence of the hypophysis, the thyroid decreases its activity; and hormones from both these glands are necessary to maintain the ovaries or testes in the normal adult condition. The hypophysis, located above the roof of the mouth and connected directly with the brain, is the most important of the lot for its hormones help to control practically all the other endocrines in one way or another. Some of the other glands are also controlled by nerves, of the autonomic system. We have already learned of this in the especially striking case of the adrenal.

The hormones, then, are highly specialized chemical messengers, formed by particular glands which are under the control of nerves or of other chemical agents, and performing important, often absolutely vital, functions in other parts of the body. If you should ask why half a dozen separate glands tucked away in unlikely corners of the body, rather than a single one, should bear the responsibility of secreting these substances, I cannot answer. Nor, for that matter, is it understood why certain particular substances which are essential for the health or even the continued life of tissue cells are not formed by them but are relegated to fellow members of the body community. There is, indeed, still considerable mystery as to the wherefore of the endocrine system, but there is also a tremendous amount of detailed and important knowledge about how it works. This, however, we cannot look into further at the moment.

THE CONSTANT INTERNAL ENVIRONMENT—I. CHEMICAL

BODY FLUIDS. Now what of the blood itself, that very important fluid which transports substances about the body? Most cells have no contact—aside from the nerves,

which reach relatively few of them, and the direct mechanical contact or pull of their immediate neighbors—with any other cells or with the outside world, except through the blood. This is not literally true, because the fluid part of the blood, the plasma, seeps out through the capillary walls to form a watery fluid, the lymph, in which the cells are actually bathed. Much of the lymph directly re-enters the capillaries to continue as blood plasma; but some passes into a separate set of vessels, the lymphatics, flows sluggishly through lymph “glands,” which add certain floating cells (lymphocytes) to the fluid, and only later, through other lymphatics, again reaches the blood stream. But this detail need not bother us here, and we can think of the plasma as directly surrounding the tissue cells. We can also temporarily neglect the cells which float in the blood stream, the huge number of red hemoglobin-carrying corpuscles, and the smaller number of white cells or leukocytes; for these normally remain within the blood channels and contribute to the tissue cells through the plasma or, in the case of the white cells, enter the tissues under special conditions of injury.

The blood plasma, then, is the world in which the body cells live. It is their whole environment, the internal environment of the body, the “milieu interieur.” It is their nurse, bringing all the food and other substances they need and removing their wastes and other products; it is their shelter, keeping them warm and wet and surrounded by the salts and other substances necessary for their normal functioning; and, with the nerves, it is their mentor, dictating their behavior. The normal life and activity of the cells is dependent at every instant and in detail on this environment; and the more complex and delicate the cell machinery, the more necessary is it that this environment remain constant and not be subject to sudden erratic changes.

THE IMPORTANCE OF CONSTANCY. Did you know that, the more accurate a clock, the more easily it is thrown out of kilter and the more carefully must it be protected

against all possible changes? The chronometers which give the standard time for the country are enclosed in heavy cases to keep out dust and moisture, are mounted on elaborate springs and cushions to keep out vibration, are buried in chambers deep in the ground to maintain constant temperature, and are driven from outside by electricity, and read the same way, to avoid disturbance by a moving person. Rather a nuisance all this, compared to the dollar watch on your wrist; but the watch serves well enough if off a minute a day, whereas the chronometers run true to a few thousandths of a second a year. In the same way, the relatively simple and unspecialized bacterial cells can muddle along in almost any sort of water and even survive in air; the somewhat fancier amoeba can put up with the moderate variations it meets in pond water, but is soon killed in the ocean; the paramecium is still more finicky and does poorly when its bath becomes slightly too acid or too alkaline; and the cells of your body, like the high-grade chronometer, demand a very special and a very constant medium, indeed.

When the plasma has too little salt in it, osmotic pressure explodes the cells; when too much, they shrivel up. If the total salt is right but the constituent kinds are in wrong proportion, other disturbances result. With too much potassium, membranes become more permeable and the cells get jittery. Remember, muscles twitch in a salt solution containing potassium but no calcium; with too much calcium, the reverse changes occur and cells become sluggish and inactive. With inadequate oxygen or sugar, cells cannot maintain their metabolism and they often enter into convulsive activity before becoming inert or dying. And so on down the list. Practically every property of blood—temperature, acidity, osmotic pressure, hydrostatic pressure,—as well as every constituent—water, salts, food molecules, gases, wastes, and such special chemicals as the hormones and vitamins—influence the body cells. Each must either be kept constant, so that the cells maintain a resting state, or be altered specifically and not at random, so that they change their activity in a manner useful to the whole

organism. And indeed the plasma does remain amazingly constant in all these attributes.

HOMEOSTASIS. This constancy does not just happen. It would hardly be an exaggeration to say that all the visceral organs and organ systems—everything except those parts of the receptor, nervous, and effector structures which are concerned with the behavior of an individual in its environment, and the reproductive system—have as their main function the maintenance of a constant plasma. (Homeostasis means keeping the self constant.) First, blood itself contains chemical systems, such as buffers, which oppose sudden changes in its acidity, oxidizing ability, and the like; second, the autonomic nervous system and endocrine and other chemical agents come into operation to oppose slight changes in the blood as soon as they occur; and third, the gross balance is maintained over longer periods by the controlled action of the great systems of viscera. This statement it perhaps just so many words to you now, but keep it in mind while we glance at the actual occurrences in the body and note how one after another of the properties of the blood stream is kept constant.

WATER REGULATION. Let us start with the simplest and most plentiful, yet most important, substance—water. Blood plasma is about 91 per cent water, and the water content of tissues varies from about 50 per cent in bone, through 78 per cent in muscle, to something over 80 per cent in brain. The amount in each remains constant within a few per cent, yet the body is not a closed sac which, once filled with water, holds it.

Loss and intake. Water is steadily being lost through the lungs in amounts varying with the temperature and humidity of the air breathed and with the rate and depth of respiration, conditions which cannot be modified to meet the body's aqueous problems. Water is also lost in very variable amounts through the sweat glands and, since this loss is necessary for cooling the body, any demands for water conservation are

again secondary. Further, urine is continuously being formed and, though accumulated in the bladder until voided, removes from the body at least the water necessary to dissolve the wastes excreted. Here then are three avenues of water loss, all inevitable for normal body functioning, yet highly variable in amount. In addition, a wound may cause considerable loss of blood, and its contained water, during a very short period. Yet through all such vicissitudes, except for a very severe hemorrhage, the water of the blood remains constant.

Of course, over any length of time, the water lost from the body must be balanced by that taken in (or produced by metabolism), so there must be some control of intake. Now, if impressed by the stories of food faddists or of dietitians, you perhaps budget the calories and kinds of food you eat, but I am certain you do not measure the water you drink. Yet your water balance has been kept far more accurately than your food balance—there are special body depots, such as fat cells, for storing food reserve, but only relatively negligible ones, such as the tissue under the skin, for storing water. Obviously, then, either you always drink just the right amount of fluid or else, if you drink too much, the excess is effectively got rid of. Mostly, you drink more water than is needed and the excess which remains after the other unavoidable water losses is drained off through the kidneys. When you do violence to the normal control of thirst and keep on drinking after thirst has been quenched, because you enjoy the taste or are trying to win a beer-drinking race, the kidneys work at an increased rate and keep the ship from foundering.

Control mechanisms. Mechanisms must exist, therefore, such that any slight decrease of the water in the blood leads to a sensation of thirst and any slight increase to an extra formation of urine. These are not fully worked out even yet, though it is known, for example, that afferent impulses which produce thirst sensations arise from the mucous membrane of the mouth and throat when it becomes slightly dehydrated. As for the kidney, a slight increase in the water of the blood reaching it automatically leads to more water excretion, as

you will see later; but, in addition to this, separate urine-forming units in this organ go into and out of activity under chemical and perhaps nervous control. One important chemical which modifies kidney action is one of the pituitary hormones. In its absence the kidney goes wild and, instead of forming perhaps a liter and a half of urine during the day, may pour out the prodigious amount of forty liters. This hormone is lacking in a disease known as diabetes insipidus, and the unfortunate victim of it is kept busy voiding urine and drinking water to allay the resulting thirst. Incidentally, this hormone is secreted from that part (the posterior lobe) of the hypophysis connected with the hypothalamus of the brain, and its production is under the control of nerve impulses; but how these are controlled, we do not know.

All this is rather crude and there must be a finer regulation, for after all it is a long time between drinks. For one thing, the water swallowed in a few seconds is absorbed from the digestive system over a considerably longer and a variable time. More important, any slight loss of water from the blood makes this liquid a more concentrated solution of various chemicals, with a higher osmotic pressure, and water promptly flows into it from the tissues. Not evenly from all, however. Water comes first from the reserves in skin and liver and then from the muscles, whereas the absolutely vital organs, such as heart and brain, remain practically unaffected. This is why a person deprived of water, still more after a severe hemorrhage, exhibits a shrunken and wrinkled skin and sunken features. Also, as you would expect, one of the most insistent consequences of blood loss is a driving thirst. Conversely, when excess water starts to accumulate in the blood, as when, for example, the kidneys fail to function properly in Bright's disease, or nephritis, the reverse process occurs; and the tissues, especially again the skin, become flooded with fluid. The loose tissue under the eyes becomes puffy first, and baggy eyelids are an early symptom of this kidney disease. If the condition persists, a general dropsy or edema develops, water oozes about below the distended skin under the pull

of gravity, and the lower portions of the body, ankles, or back, as the case may be, become bloated.

SALT REGULATION. Let us look next at the salts, or rather at the salt ions. Calcium, potassium, and sodium are the main positive ions; chloride the main negative one.

Calcium. Calcium is taken into the body in variable amounts in the food and, of course, if insufficient the body can do nothing about it except conserve what it has. A diet deficient in calcium is not so serious in an adult, whose bones are completed (except in a pregnant woman whose body must supply calcium for the growing fetus), but plays havoc with the growing child, who needs large amounts of lime salts (and phosphate) to build its bones. Inadequate calcium (or phosphate) leads to rickets and the consequent malformations of the softened bones. Milk, especially rich in these substances, is consequently a particularly good food for growing infants; and of course that is just what it was "designed" to be. But having enough calcium in the diet is only the beginning, for it must be absorbed, kept in the blood in proper amounts, deposited in the bones if need be, and the excess excreted, partly in the urine, partly through the lower intestine into the feces.

You were probably fed cod-liver oil as a youngster, and will most likely feed it to your children, unless at that time the vitamin D which the oil contains, and which already is available in purified form, becomes a lot cheaper. Vitamin D, or calciferol as it is now called, is necessary for the proper absorption of calcium and particularly for its deposition in bone. Since human beings have taken to covering their bodies with opaque clothing, the vitamin must usually be added to their diet from outside sources; but primitive man, who certainly ate relatively little liver and who wouldn't have understood about vitamins even if he had heard of them, would have fared pretty badly had he not been able to make this substance in his own body. Vitamin D is formed by the action of sunlight upon a closely related substance, widely present

in living tissues, and so is made during the day when and where the skin is exposed to light. (A bird's feathers, like our clothes, stop the light; and no blood flows through these structures for, like our hair, they are composed of dead cells. Yet birds also need calciferol. You have seen ducks or geese solving this problem, while preening themselves. A gland near the tail secretes the parent substance, the bird spreads this over its feathers with its beak, the sun changes it to calciferol, and the supply of vitamin is gathered in.)

The fine control of the calcium in the blood depends mainly, however, on an entirely different substance, parathormone, the hormone produced by the parathyroid glands. These glands lie imbedded in the thyroid, lying on either side of the neck below the Adam's apple, and when surgeons first began to remove the thyroid in goiter cases these went with it. The results were dramatic and distinctly unpleasant. After two or three days the parathyroidectomized man (or dog) began to twitch, soon went into spasms, and shortly died in terrific convulsions or tetany. For decades physiologists worried about the cause of the severe symptoms and death until it was finally discovered, in animal experiments, that the calcium of the blood steadily fell in amount after the parathyroids were removed. The amount normally present seems quite trivial, only 10 milligrams in 100 cubic centimeters of blood, yet when this is decreased to 6 milligrams the convulsions follow. And injecting sufficient calcium to restore the normal blood concentration promptly stops the convulsions. A similar, although less severe, calcium lack develops in infants who cannot retain or digest their milk and it produces the condition of spasmophilia, a general increased irritability and jumpiness with some twitching.

It was later discovered that an excess of parathormone increases the blood calcium, just as a deficiency lowers it, and the symptoms, as you might expect, are somnolence, lassitude, and weakness. But where does this extra calcium come from, since the blood increase occurs even when the diet is actually free of it? It is leached out of the bones by the blood carrying

the hormone and, if the condition continues, as in cases of tumor of the parathyroids, the bones become weak and break on slight provocation. The parathyroid more normally increases its activity during pregnancy, possibly under the influence of the hypophysis, and the high calcium in the maternal blood thus insures the normal development of the fetus; but unless the mother is careful to eat calcium-rich food during this time her bones and teeth pay the price.

Potassium. Potassium acts oppositely to calcium; and it is really the balance between the two, rather than the concentration of either alone, which is most important. Since practically all the salts of this metal are soluble, it contributes little to the solid structures of the body, but it is the main positive ion of the semi-fluid protoplasm within the cells. In the blood plasma and similar body fluids there are only 20 milligrams of potassium per 100 cubic centimeters, but over 800 of sodium. In the tissues, however, for example within muscle cells, the concentrations are almost completely reversed. If the blood potassium rises, brain and muscles are first stimulated; but later, if it becomes high enough, they are paralyzed. There is ordinarily little difficulty in its supply, for potassium is richly present in both plant and animal food; and any excessive amount taken is excreted by the kidney. Yet even this common substance is partly regulated by a hormone of the adrenal gland, one produced by the outer shell or cortex of the gland rather than by the core or medulla which is responsible for adrenalin. When the adrenal cortex is removed, the blood potassium steadily increases (and blood sodium as well, since much water is lost through the kidneys) and its high concentration contributes to marked symptoms which finally terminate in death.

Sodium. Sodium chloride, overwhelmingly the most common salt in the blood plasma, is taken freely in our diet, even if we do not deliberately salt our food, and is continuously lost in the urine and to some extent in sweat and tears. Excesses are removed by the kidney. (But with damaged kidneys, salt gradually diffuses into the tissues and exaggerates the

accumulation of water there; hence salt is severely restricted in the diets of nephritic patients.) A deficiency is unlikely to occur in meat-eating animals, but the herbivores, eating potassium-laden plant cells and having no sodium-rich blood to drink, must often supplement their diet from salt licks. When their body sodium starts to decrease they develop a salt-hunger—presumably akin to the sudden craving for chocolates or what not which occasionally attacks most of us, but far more severe—and off they go for salt. Carnivores often lie in ambush at these licks and the herbivores seem to realize that these places are dangerous for they approach them with great caution, yet go there they do for the need of salt is imperative.

GLUCOSE REGULATION. As for water and for salts, so for the bulk of other plasma constituents. Protein, constituting 7 per cent of this fluid, is formed primarily in the liver, normally remains constant, and helps control the effective osmotic pressure of the blood. Amino acids and fats, on the way in from a digested meal, show moderate fluctuations, yet remain present through long periods of complete starvation; the wastes, such as urea, ammonia, and creatine, are removed by the kidney as rapidly as they are formed; and the gases, oxygen and carbon dioxide, will demand special consideration later on. But we cannot leave the control of blood chemicals without looking at the especially important and interesting case of glucose. For this sugar is the primary fuel of most, if not all, cell metabolism and must be continuously available in proper amounts.

The blood glucose normally remains close to 0.1 gram per 100 cubic centimeters, although it may increase somewhat above this for a short while after a starch-rich meal. It is not excreted by the kidney until the amount in the blood is far above normal, so that only in extreme cases does this organ contribute to its regulation. When the blood sugar falls to half its normal value, convulsions and coma result and may end in death. Obviously such a fall does not occur, even when

no food is taken during days or weeks. In the absence of a safety valve like the kidney, and with no external source of supply, and although it is continually being used up all over the body, the blood glucose yet remains at its proper level.

Glycogen storage. One immediate conclusion is: Since muscle and other cells take glucose out of the blood, sugar must come into it from somewhere. How would you find its source? By chemical examination of every organ for a large store of glucose? You will be disappointed. There is a little in each but no more than could have come from the blood at the time. This is hardly surprising, since glucose is freely soluble and easily diffusible, and any large amount present in a cell would soon dissolve out into the surrounding blood. Then glucose must be formed somewhere from something else. It is almost a century since its precursor was discovered in the liver by the great French physiologist, Claude Bernard (also the first clearly to recognize the importance of the *milieu interieur*). The freshly removed liver of an animal, he showed, contains little or no glucose but large amounts appear in it upon standing. At the same time, an insoluble starch-like substance, which can be tested by the brown color it gives with iodine, disappears. This glucose-former, or glycogen, is present as insoluble granules in the liver cells, very much more in those of a recently fed than of a starved animal.

When you eat a meal, the carbohydrates in it are digested to glucose and this is absorbed through the mucous membrane of the gut wall into the blood flowing through. But the venous blood from the intestines does not go directly to the heart, and then around the body; all of it passes first to the liver. It is simple to show by direct chemical analysis that most of the extra glucose is taken out of the blood by the liver, for the concentration of this substance is lower in the veins leaving the liver than in the portal vein entering it. And of course the glucose taken up is largely built into glycogen and stored in the liver cells for future use. The need for it soon arises, as soon as no more glucose is being supplied by

the intestine. Analyses made at this time show that the blood entering the liver contains less sugar than that leaving.

How important this steady supply of glucose from the liver actually is, is shown by the results of removing this organ. The dehepatized dog recovers from this serious operation quite well; but his blood sugar rapidly falls, and in ten hours or so he will be dead from coma or convulsions unless a glucose solution is steadily fed into his veins. Actually, this part of the story is far more complicated, for the amount of glycogen stored even in a well-fed liver (plus the smaller concentration, but considerable quantity, in other tissues) could not continue to supply the sugar needed by the body for more than a day or two; yet animals or men survive far longer periods of starvation. More carbohydrate is formed in the liver from the fat reserves of the body and even from proteins. But let us leave this to see first how the blood glucose is kept so constant despite all the variations in its supply and use.

The role of insulin. The most important single factor which controls the metabolism and concentration of glucose is the hormone, insulin. Long before this substance was discovered and purified, it was found accidentally, during experiments on the role of the pancreas in digestion, that depancreatized dogs developed diabetes. The story has it that an investigator removed the pancreas from an animal and then went on his vacation, leaving the dog in the care of his laboratory helper. This man kept his eyes open, for he noticed that ants formed a trail to the bottle in which the dog's urine accumulated; and he thought about what he saw, for, knowing that ants seek sweets, he tested the urine for sugar and found a great plenty of it present. Now sugar in the urine is an important symptom of the disease, diabetes (really diabetes mellitus, meaning a flowing through the body of sweet substance), and further examination of the animal showed that it had indeed all the symptoms of this condition.

In diabetes, the sugar in the blood increases to two, three, or more times the normal concentration and large amounts

are excreted by the kidneys, along with the considerable quantity of water needed to carry it. The animal correspondingly has an exaggerated thirst and drinks water copiously. Despite the plentiful supply of glucose to the tissues, they behave as if starved, indicating a disturbance or loss of their ability to burn the sugar. The animal is ravenously hungry and eats prodigiously, yet it progressively loses weight and wastes to a shadow of itself before dying. If insulin is administered regularly all these symptoms disappear, glucose metabolism becomes normal, and the man or animal with diseased or absent pancreas gets on quite comfortably. (Ultimately a fatty degeneration of the liver may develop, but this is another story.) When too much insulin is injected the blood sugar falls, as you might guess, and if the hypoglycemia (decreased sugar in the blood) is severe enough, the expected coma and convulsions ensue; but they can be abolished promptly by the injection of glucose. Such dramatic treatment with insulin is now being used in certain kinds of insanities.

Control of insulin secretion. Obviously, then, one means of controlling blood sugar is the amount of insulin secreted by the pancreas; but what, in turn, controls this? Increased insulin secretion lowers blood sugar, so, if an increase of blood sugar stimulated the secretion of this hormone, regulation would be automatic. And there is some evidence that this is the mechanism, although the increased blood sugar does not act directly upon the pancreas but rather upon the brain, probably the hypothalamus. It causes an increased activity of the vagus nerve (parasympathetic), some of whose fibers go to the pancreas and make it secrete insulin. The other phase of regulation is more complex, for apparently there are no nerves which inhibit insulin secretion. This hormone, therefore, is continuously entering the blood, and the amount cannot be lessened to compensate for a fall in blood glucose. Hypoglycemia does, however, stimulate other parts of the hypothalamus which connect with the orthosympathetic nerves. Some of these go directly to the liver and cause a breakdown of its

glycogen to glucose, which is promptly dumped into the blood. Another orthosympathetic nerve sends a branch directly to the adrenal medulla and, when active, causes a generous secretion of adrenalin. Some of this reaches the liver and, acting like orthosympathetic stimulation, also leads to glycogenolysis and so further insures an added supply of the needed glucose to the blood.

The hypophysis and glucose origin. Another unexpected discovery, hardly a decade ago, further complicated the story;

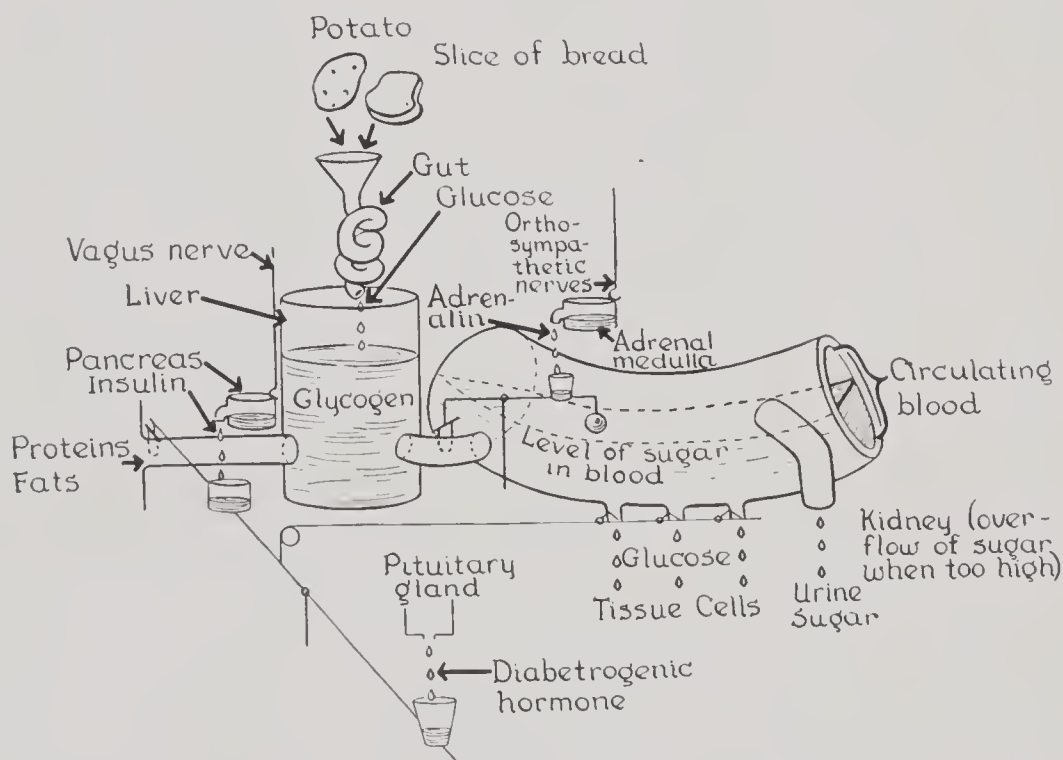


FIG. 36. A mechanical model illustrating the main body devices for keeping constant the concentration of sugar in the blood. See text for details. (Drawn by E. M.)

for it was found that if first the hypophysis was removed and then the pancreas, little or no diabetes resulted. Obviously some substance from the hypophysis as well as insulin from the pancreas is involved in sugar metabolism; and indeed the pituitary hormone seems to be the more immediate cause of the sugar disturbances. Insulin is necessary merely to balance or counteract the action of this "diabetogenic" substance, for when the latter is absent insulin can be spared. This finding also throws some doubt on the conclusion that insulin acts by

enabling tissues to burn sugar, and we must look again at the origin and fate of this substance.

When diabetes is produced by removing the pancreas from an otherwise normal dog, not only does an excess of sugar appear in the urine but also a large amount of nitrogen, mainly as urea. Such urinary nitrogen is produced by the metabolic breakdown of proteins; and the further facts, that the nitrogen and sugar in the urine appear in fairly constant proportions and that a great deal of extra sugar is somehow being produced in the body (for the high blood sugar (hyperglycemia) and sugar overflow into the urine (glycosuria) continue even when no sugar is fed), strongly indicate that large amounts of protein are being converted into glucose. Perhaps, then, the obvious tissue starvation in diabetes is not so much due to an inability to burn glucose as to some other defect consequent on protein loss. The new formation of glucose from protein, gluconeogenesis, shown to occur largely in the liver, might, then, be brought about by the presence of the pituitary diabetogenic hormone and be prevented by insulin.

I have purposely stated the above very conditionally, because these questions are still being intensively investigated and many facts seem to favor the alternate interpretation of diabetes, as a disturbance in the burning rather than in the production of glucose. Furthermore, we have not looked at the important cycle of exchange between the liver and muscles. It is known that some of the lactic acid formed during severe exercise diffuses from the muscle into the blood, is captured by the liver, and is there rebuilt into glycogen; and the glucose liberated into the blood from liver glycogen is in turn partly taken up by muscles and built into their own small store of glycogen, to be used again in the metabolic changes of rest or contraction. Even in this sketch, however, it is apparent that three endocrine glands, both portions of the autonomic nervous system, and the central nervous system as well, all contribute to the apparently simple matter of keeping blood glucose at its proper concentration!

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CHAPTER V

INTERNAL INTEGRATION (*CONTINUED*)

THE CONSTANT INTERNAL ENVIRONMENT—II. PHYSICAL

TEMPERATURE REGULATION. Let us look next at the body devices for keeping constant one of the physical properties of blood, its temperature. The mammals and birds, alone of all animals, maintain a constant temperature; that of all others varies with the temperature of the environment. Since the speed of cell metabolism and action varies markedly with the temperature, it is of great advantage to be warm-blooded and so not slowed by the cold. You have noticed how sluggish insects and worms and other cold-blooded animals are in cool weather as compared to their behavior on a hot summer day. But you and Fido are, if anything, more lively and alert. Further, warm-bloodedness means not only the ability to stay warm in cold air, but also that of remaining at constant temperature, 98° to 99° Fahrenheit for man, even when the surroundings are much warmer. A striking experiment to demonstrate this was performed a century and a half ago, when a man carried some raw beefsteaks into a room overheated by closed stoves. The beefsteaks were laid on a wooden table and the man sat in a wooden chair; in time the dead meat was cooked through while the living meat, quite uninjured, carried it out.

Heat production. Obviously, then, your body must be able to produce heat for keeping warm and to lose heat for keeping cool; and its temperature is kept constant by this continuous balance. Of course, the steady burning of food in the body cells liberates energy, which finally becomes heat. Even with complete muscular rest, after relaxing on a bed for half an hour, and when the intestinal tract is not busy digesting,

18 hours after the last meal, the basal metabolism, as it is then called, is about 1800 calories of heat per day for the average adult. (Metabolism is more accurately expressed as the number of calories generated per hour per square meter of body surface, and this value is quite constant for normal adults, at about 40 calories. It is higher in children.) But we are not normally lying about in a hungry condition; we are performing a moderate amount of muscular work. This, we have seen, is attended with a large liberation of energy, and a man doing heavy labor may require 5000 calories or more a day. Most of us use something under 3000. Here, therefore, is one obvious way in which heat production can be controlled, by increasing or decreasing muscle contraction.

The normal postural contractions are maintained, you know, by impulses from the spinal cord. It will not surprise you to learn that when the skin is hot, still more when the blood to the brain becomes a trifle warmer, these nerve impulses are decreased and the muscle tone is diminished. From the relaxed muscles, in turn, come fewer proprioceptive sensations—the main reason you feel so lackadaisical in hot weather. When you jump into a cold shower, on the other hand, reflexes from skin receptors make your muscles tighten up and give quick twitch-like contractions; that is, you shiver. Shivering can also be produced, even though the skin remains warm, by cooling the blood going to the brain. Incidentally, it is because of the continued extra muscle contractions in cold weather that you feel tired, and develop a good appetite, after a day in the open.* Finally, it has been demonstrated in some animals that the thyroid gland enlarges in cold weather, a slower adjustment to increase body metabolism and heat.

Heat loss. So much for the regulation of heat production; what of heat loss? Being ordinarily warmer than its surroundings, the body loses heat as does any other hot object by radiation, convection, and conduction. The last two of these depend upon the surrounding medium—metal conducts rapidly

* The sensation of hunger arises from contractions of the stomach; how would you go about finding the mechanisms which control this?

and therefore feels cold whereas air, if unstirred, conducts very poorly indeed—and all three depend on the actual temperature of the hot object. Heat is lost only from the surface, so if less blood were circulated through the skin, although this might cool down some, the temperature of the blood and deeper organs would not fall so rapidly. The skin acts rather like the radiator of an automobile, cooling the blood that flows through it, and when less blood flows the “radiator” gets cooler but the “engine” hotter. Thus, when either the skin or the blood to the brain is cooled, the same mechanism, operating through autonomic nerves, constricts the skin vessels; and the reverse changes make the vessels dilate. Try this for yourself. Fill one pan with cold water, iced if convenient, and another with hot water, but not hot enough to hurt you; place one hand in each, and, remembering that more blood makes the skin redder, less, paler, watch the color changes in your skin.

All this, however, is not good enough to keep up body temperature; and there is the further danger of the relatively bloodless skin being frozen and injured. The two classes of vertebrates, birds and mammals, which keep up their temperature and activities through the winter, have developed special protective coverings, feathers or hair. A fur coat or a feather puff keeps you warm because, in each case, a mesh of entangled threads holds the air fixed in its loose pockets, and this stationary air is an excellent heat insulator. To be sure, you put on a coat in cold weather and take it off when warm, and your pet cat or dog grows a heavier pelt in winter than in summer; but neither the mammal nor bird can change its covering from moment to moment, as the temperature alters.

Remember how fluffy kitty looks before she comes in from the cold, and how sleek after sitting by the fireside, and you know how the animals have solved this problem. Tiny muscles in the skin connect to the base of each hair, and when they contract the hair is moved like a lever and stands out straight from the skin. (These muscles remain in your skin even when the large hairs are missing, and their contraction

produces the little bumps collectively known as goose-flesh.) The rest is obvious. Orthosympathetic nerves control these muscles, and discharges down these nerves are set up in the same way as are messages down those to the skin blood vessels. In the cold, the sheath of hair around the mammal, or the feathers around the bird, is fluffed up and made much thicker and the insulation is greatly improved.

All these mechanisms, acting together, do very well in keeping the body at a temperature above that of its surroundings, but none of them could keep it at a lower temperature. To be sure, with completely relaxed muscles to minimize heat production and with flattened hair and dilated skin vessels to maximize its loss, body temperature might remain only a little above that outside, but it could never fall below. This last requirement of regulation is met by evaporating water. It takes less than 1 calorie to heat water from 99 to 100° C., but it takes 560 calories to turn this gram of boiling water into steam at the same temperature; that is, to evaporate it. A similar relation holds at lower temperatures; and you have probably wrapped thin wet towels around yourself to keep you cool as the water in them evaporates. The body does this continuously by forming on the skin surface a moist film of sweat, which cools as it vaporizes. The warmer the weather, the more the cooling needed, and the more the perspiration formed, again under the control of the autonomic nerves and of the temperature-regulating brain center in the hypothalamus.

Man is one of the few mammals which are supplied with sweat glands over the whole skin. The dog and cat, for example, have them only on the foot pads. These animals cool themselves by evaporating water from the mouth and tongue, and it is to increase this evaporation that they pant continuously when warm. Incidentally, when you are losing a great deal of water through the sweat glands—and you can lose several pounds during a few sets of strenuous tennis in hot weather—you naturally develop a most satisfactory thirst, and at the same time produce but a small amount of highly concentrated urine.

One last point, of the many not touched upon. Sweat contains salt in addition to water, you know how it tastes, and if only the water loss is replenished when we drink, the blood can become impoverished in sodium chloride. It is this sweating of salt water and drinking of pure water which cause one form of collapse. Heat prostration of persons doing heavy work under hot conditions is now prevented by having them swallow little pills of sodium chloride along with that refreshing drink.

PRESSURE REGULATION. A blood, constant in chemical and physical properties, is of no use to the cells except as it reaches them. We saw earlier some of the machinery which regulates the amount of blood passing any particular group of cells, and we were concerned then about the possible consequences of a general vessel dilatation. Flow through any vessel will vary with that vessel's caliber only when the driving head of pressure is maintained uniform. Only as the water pressure in the city mains is kept constant can we satisfactorily regulate the flow from any one faucet by the degree to which we open the tap. How, then, is blood pressure kept constant?

Cardiac output. From the heart, blood is pumped into the aorta, carried on into the other large arteries (of which the two carotids supplying the head must be mentioned), led into the smaller and smaller twigs of the branching arterial tree, until it passes through the fine arterioles into the capillaries. The arterial tubes have thick elastic walls, except the smallest ones, which are thick and muscular, so that the arteries serve merely as conduits, allowing no exchange between blood and tissue. All the active interchange takes place during the second or two in which the blood flows through the fine, thin-walled, membrane-like capillaries. From these the blood, no longer under high pressure, seeps into venules, and the separate rivulets gather in ever-larger veins, until the two great vena cava empty the stream into the heart. It need not concern us now that the venous blood from the body enters the right auricle, then ventricle, and is pumped by this through a similar but

smaller set of arteries, capillaries, and veins of the lungs to the left auricle. It is the left ventricle, into which the left auricle

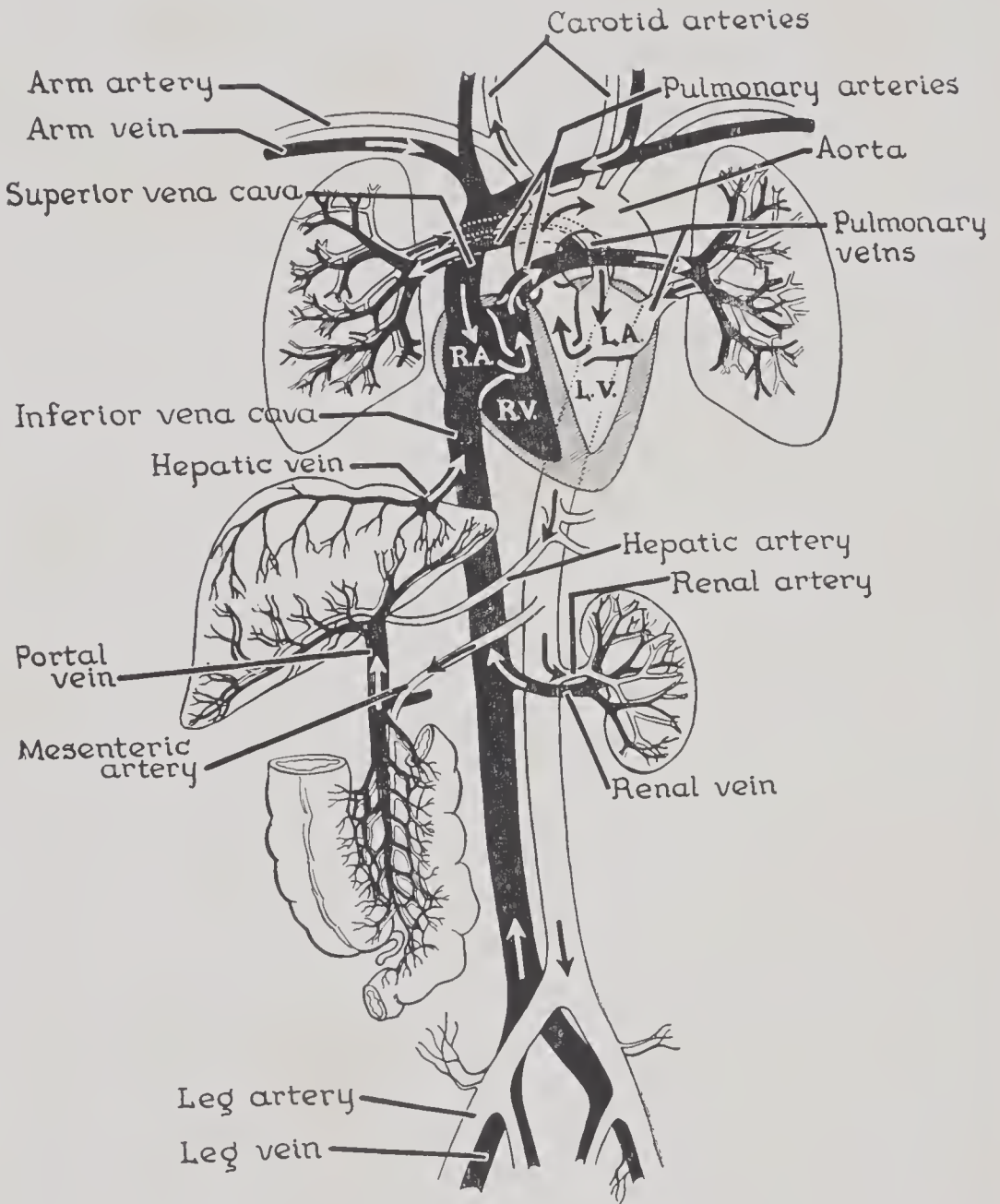


FIG. 37. Diagram of the main vessels in the circulatory system. The venous blood entering and leaving the right heart is shown black; the aerated arterial blood on the left side is white. Note the completely separate circuit through the lungs, from right ventricle to left auricle, and the peculiar arrangement in the liver. This latter receives arterial blood in the usual manner but, in addition, the venous blood from the intestine reaches it through the portal vein and is distributed through an additional set of capillaries. (Drawn by E. M.)

empties, which sends the blood around the body. We can also neglect the small pressure in the veins, although this may in-

crease under various pathological conditions and so retard the flow through the capillaries; and the second-to-second variations in arterial pressure, the pulse, which results from the intermittent pumping of blood by the heart, beat by beat.

Your arterial blood pressure under ordinary conditions probably fluctuates from a value equal to the pressure of 120 millimeters of mercury, systolic (that is, at the end of a heart contraction, or systole), to one of 80 millimeters of mercury, diastolic (at the end of the cardiac pause after relaxation, or diastole), and so averages around 100. The pressure will obviously fall if the cardiac output per minute is decreased, as when the heart beats more slowly or ejects less blood at each beat, or if the blood can run out of the arterial tubes more easily. The cardiac output depends, of course, on the rate and strength with which the heart beats, but also on the amount of blood flowing back into this pump from the veins; and the output will fall when either the heart is less active or less blood reaches it.

Peripheral resistance. The arteries are kept continuously overfilled with blood, and the recoil of their stretched elastic walls, like that of a blown-up rubber balloon, keeps their contents under pressure. If the balloon leaks, the pressure in it will be maintained only while air is forced in as rapidly as it leaks out. But blood constantly leaks from the arteries through the open arterioles and capillaries, and only because more is pumped in by the heart, as much as flows on through the capillaries, does the pressure stay up—after the heart stops, a few seconds suffice to bring arterial blood pressure to zero. It is the small-calibered arterioles and capillaries which offer resistance to the free flow of blood around the circuit; it is in these that the pressure falls sharply from the high value in arteries to the low one in veins; it is these many fine openings which correspond to holes in the distended balloon; and it is, therefore, the caliber of these vessels which determines how rapidly the blood leaks out from the arteries. The second great factor, then, besides cardiac output, which controls blood

pressure, is peripheral resistance, the collective size of the arteriolar and capillary channels.

It is true that local chemical conditions can make the capillaries enlarge or shrink, but their walls contain no smooth muscle and normally the flow through them is mostly controlled by the dilatation or constriction of the muscular arterioles. Now, with a continuous opening and closing of arterioles and capillaries, to bring more or less blood to cells all over the body as they are active or resting, with the amount of blood returning to the heart dependent on its flow through these small vessels (and when large numbers of them are open at once, as those in the viscera in certain kinds of shock, they can actually hold all the blood of the body, so that little or none returns to the heart), with the heart beat subject to change through nerves and chemicals and temperature—*how* is the blood pressure held constant?

Reflex control. Suppose we suddenly withdraw a large amount of blood and so lower the blood pressure. Fluid from the tissues will, we have seen, enter the blood vessels and bring up the blood volume. But this requires minutes or hours, yet the blood pressure returns to its original level in a few seconds. This prompt return is achieved by the heart beating more rapidly and strongly and by a general constriction of arterioles throughout the body. The vessels constrict and the heart works harder, because the orthosympathetic nerves to them, vasoconstrictors to the arterioles and accelerators to the heart, are carrying more messages; while at the same time the parasympathetic nerves, vasodilators to the vessels and vagus to the heart, decrease their continuous moderate inhibition. The heart and vessels are thus both pushed and pulled into their responses.

Such coordinated increase and decrease in the discharges along many nerves about the body at once suggest coordinating centers in the brain which control them; and cardiac and vasomotor centers do lie, close together, in the medulla. There they can be directly stimulated with electric currents, for example, and indeed call forth such responses. But how are these

centers naturally thrown into appropriate activity? By afferent impulses reaching them from interoceptors located in the walls of the vascular system. As you would expect, there are two sets of these, working in opposite directions. One group, in the aorta and carotids, is stimulated to greater activity when the blood pressure rises and decreases its activity when the

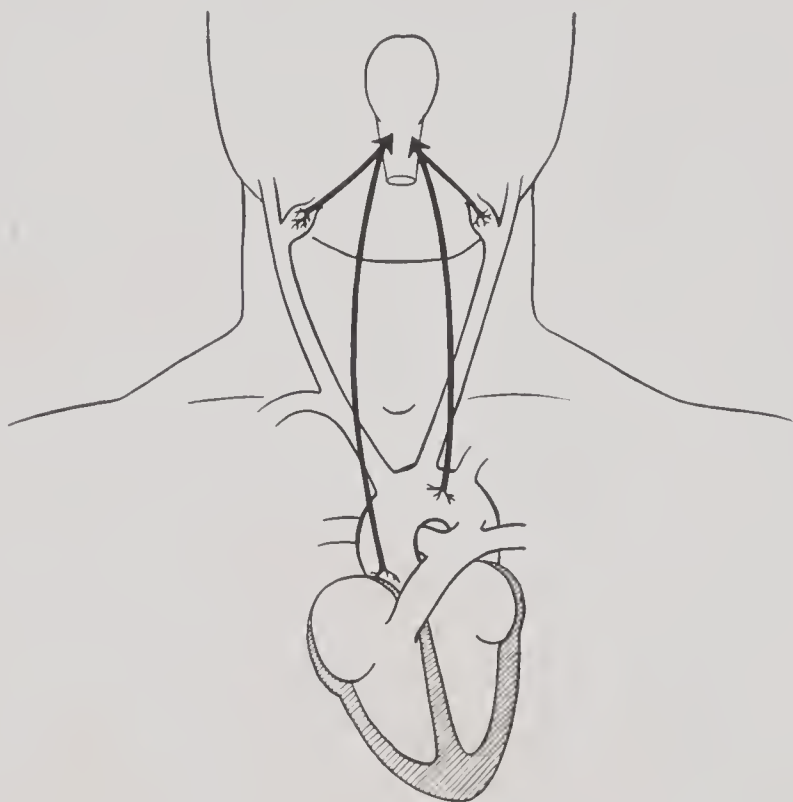


FIG. 38. Some sensory nerves, from carotid sinuses (carotid nerve) and aorta (depressor nerve), act on the vasomotor centers in the medulla to lower blood pressure reflexly. The efferent nerves of this reflex—to dilate blood vessels and to slow the heart—are not shown; but the cardioinhibitor fibers, like the depressor ones, run in or with the vagus. Other sensory nerves, which reflexly raise blood pressure, arise from many receptors in blood vessels, viscera, and skin and are not shown. (Drawn by E. M.)

pressure falls. The nerves from these, depressor and carotid sinus nerves respectively, reach the medulla; and the impulses they carry act reflexly on the cardiac and vasomotor centers to produce increased action of the vagus and vasodilators and decreased action of the accelerators and vasoconstrictors, and by all these means lower blood pressure. The other group of receptors, widely present in peripheral vessels, is stimulated as blood pressure falls; and the afferent nerves from them,

the pressor nerves, act on the medullary centers in exactly the reverse way, to produce a rise in blood pressure.

This may sound complicated, but only because the body, like a careful engineer, multiplies its devices to be sure of achieving the desired result. In essence the process is as simple and direct as it well can be. An increase of blood pressure sets up afferent nerve impulses which reflexly cause those changes in heart and blood vessels which lower blood pressure; and the reverse changes follow a pressure fall. As long as the apparatus is in working order it is completely self-regulated and the general arterial blood pressure remains constant. Note further that the pressure will be maintained despite considerable changes in vessel size and blood flow in particular tissues or organs, and even despite considerable changes in the volume of blood which is actually circulating. It is this combination of constant arterial pressure and local turning on and off of the small vessels, in accord with the metabolic need of the cells they supply, that makes our circulation so efficient.

CLOTTING AND REPAIR. The blood is a highly important fluid, yet not so terribly precious in the sense that the body has difficulty in making it. You could lose, perhaps, a third of your blood and, aside from temporary thirst and weakness, be little the worse for it. In fact it is possible to remove over a third of a dog's plasma every day or two for long periods of time and have him continuously make good the deficit. (This is done by bleeding, centrifuging out the blood cells, resuspending them in proper salt solution, and reinjecting. The most important constituent lost in this process is the plasma protein. Such experiments have shown that the liver is important in manufacturing these proteins and have measured the rate at which it can make them.) But it would go ill with you, indeed, if half or more of your blood were rapidly lost through a bad wound, as when an artery is cut or torn; for then the venous return to the heart is so poor that, even though this beats valiantly, the blood pressure falls and the circulation stagnates. Further, with a large artery open, if blood pressure

were able to stay up, blood would run out through the big leak, and if the pressure fell, so that the blood failed to circulate, results would be almost as bad as with the blood gone entirely; for the mere presence of stagnant blood around cells does little good.

Fibrin formation. Yet closed pipe systems spring leaks, sooner or later, and animals are often wounded by their own clumsiness or the attacks of others. There is needed, then, some method of plugging any leak that forms in the vascular bed. You are familiar with part of this story; blood is able to clot. The actual clot is a gelatinous mass produced by the change into an interlacing set of protein fibers, fibrin, of one of the blood proteins, fibrinogen. (This fibrin-former constitutes only some 1.5 per cent of the blood protein, or 0.1 per cent of the blood plasma.) Clotting is primarily a colloidal change of this protein from the sol state to the gel state, comparable to the gelling of gelatin. But now the trouble begins, because fibrinogen is always present in the blood, yet this fluid never normally coagulates while in uninjured vessels. Something must be added to cause this change or else something normally present which prevents clotting must be removed. Some simple experiments will carry us further.

Draw a few cubic centimeters of blood into a test tube and let it stand until it clots. If the test tube is quite clean and smooth and the temperature that of an ordinary room it may take as much as half an hour before this happens; but let the tube stand for some hours. A good clot will then have formed and, again like gelatin, will have shrunk a little and left outside of it a clear pale yellow fluid, called serum. Serum will, of course, contain no fibrinogen—that has all been converted to



FIG. 39. A blood clot standing in a test tube slowly shrinks and pulls away from the wall. The clear yellowish fluid squeezed out from the fibrin mesh is the serum.

(Drawn by P. McC.)

fibrin in the clot; but if another substance had appeared to cause this transformation some of it may have remained in the fluid. The test is simple. Draw another sample of blood into a fresh test tube and add some serum from the first clot. Instead of requiring half an hour, clotting occurs almost at once. Further, if the serum is heated before making this test, the acceleration of clotting fails to occur. It follows that a substance has been formed in the shed blood which is able to turn fibrinogen into fibrin. It is called thrombin; because a blood clot which forms inside a blood vessel, as a result of infection or other injury of the vessel walls, is called a thrombus. That it does indeed have this action is shown by mixing purified solutions of thrombin and fibrinogen, for the mixture promptly clots.

These results do not, however, prove that the alternate possibility, of a substance which prevents fibrin formation, is wrong. As a matter of fact, substances are known which prevent the interaction of fibrinogen and thrombin, hence called antithrombins, and which keep blood indefinitely from clotting. The leech, for example, makes a tiny skin wound and feeds on the blood which oozes out. If the blood clotted, its dinner would be cut short; this undesirable result it prevents by secreting and introducing into the wound just such an antithrombin—hence leech bites are difficult to staunch. But to return to our blood; clearly thrombin is not ordinarily present in it, else it would clot without waiting to be shed. So we must start again, and find out where the thrombin comes from.

Thrombin formation. When blood is drawn directly into a concentrated solution of certain salts it is prevented from clotting; but after some time a flocky precipitate forms. This solid is not thrombin and will not clot blood, but when treated in the manner to be described it turns into thrombin. Hence its name, prothrombin. We are now one step further, but clearly still not at the end; for in the circulating blood prothrombin does not change into the active thrombin. Again we might think that substances which prevent this reaction are present; and indeed antiprothrombins are present in small amount at

all times. Perhaps they are formed in the liver; at least liver extracts have been made which powerfully prevent blood clotting, partly by acting as an antiprothrombin.

But still something positive is also needed; and at last we have reached the crux of the whole mechanism. It is after encountering injured tissues that blood clots. Presumably, therefore, some substance liberated from the inside of cells when they break down is able to activate prothrombin and start the ball rolling. This is easily confirmed by adding the fluid from almost any crushed tissue, or bits of the crushed tissue itself, to fresh-drawn blood. It clots promptly. This prothrombin activator, thrombokinase, then, is the missing ingredient from the clotting recipe. Normally absent from blood, it is produced by the breakdown of practically any kind of cell. And still the story is incomplete.

Blood drawn from a clean-cut artery into a clean test tube may require half an hour to clot, but you know perfectly well that a small cut in your skin stops bleeding in two or three minutes. That this rapid coagulation does not depend on the blood remaining in the wounded tissues is shown by letting drops of it fall on an ordinary surface, say of glass, for these drops also clot in a short time. Why, then, does blood clot so much more rapidly when handled without special care than when kept in contact with clean and smooth surfaces? And, for that matter, why does blood drawn from the inside of an artery through a hypodermic needle, without touching injured tissue, ever clot? Something in the blood itself must also be able to form thrombokinase when it is handled a little roughly; and since this kinase is formed by the injury of tissue cells, we might seek its origin similarly in the blood cells. Actually the white blood cells can produce it, but they are not its important source, and the red cells are practically useless.

A third type of formed element in blood can be seen under the microscope, one much smaller than the other cells and probably not a true cell at all; it is called a platelet. There are a great many of these present, about 300,000 in a cubic millimeter, as compared with 7000 white cells and 5,000,000 red,

and they disintegrate to liberate the thrombokinase. Within the blood vessels they break down slowly or not at all, but when the blood comes in contact with foreign substances, especially rough or dirty surfaces, they disintegrate rapidly; and the rest of the changes follow promptly. One of the difficulties in hemophilia, the disease in which people bleed interminably after any trivial injury, is that the blood platelets are abnormal and fail to decompose and yield up their thrombokinase as they should. Now we seem to have an adequate mechanism for stopping hemorrhage from an open blood vessel; but caution now, for the body always has more tricks up its sleeve.

When fibrinogen, prothrombin, and thrombokinase are all abundantly present and antithrombin and antiprothrombin are completely absent, blood clotting can still be prevented entirely by removing the calcium ions from the blood. This is easily done by adding sodium citrate, for example, which combines with the calcium ion and effectively prevents its action. This is the device commonly used to prevent clotting when blood samples are taken for laboratory analyses or when larger quantities are used for transfusion, if not immediately passed from one person to the other. The citrate acts only by removing calcium, for adding more calcium ions after the citrate promptly induces coagulation. Use your scientific ingenuity to plan the experiments needed to show just where in the clotting mechanism calcium is required. You can even perform them with no special facilities. I will tell you the answer—thrombokinase and prothrombin react to form thrombin only when calcium is present, whereas thrombin and fibrinogen react to form fibrin just as well whether calcium is present or not.

There are still plenty of complexities we haven't touched. For one thing, in order to form prothrombin, the body must have a supply of a vitamin, the antihemorrhagic vitamin, K, in the absence of which a condition somewhat like hemophilia develops. Further, vitamin K must not only be present in the food, it must also be successfully absorbed from the gut. This seems to require the presence of still other substances, the bile salts, normally carried in the bile from the liver or gall bladder

into the intestine. If the vitamin is missing or if the bile ducts are obstructed, the formation of prothrombin is interfered with and a strong tendency to continued bleeding results.

Scar formation. A last point about clotting is worth mentioning here. Once the coagulum is formed, hemorrhage is stopped, right enough; but a pretty flimsy dam is holding back the blood, and a little moving about will break it down and start bleeding all over again. With the passage of days, however, this is no longer true. The wound heals, and a tough scar remains in place of the soft clot. Certain of the blood white cells (macrophages) which have been entangled and stagnant in the clot undergo remarkable structural changes; they metamorphose from small round free-floating cells to large elongated fixed ones, which form tough interlacing fibers about themselves. These fibroblasts and their fibers are the same structures that constitute much of the binding or connective tissue normally present throughout the body; and one of the functions of this type of white cell, one of the reasons it is carried in the circulating blood, is to be present in the wound and to help repair the injured tissue. Although the connective tissue fibers are different from and tougher than those of fibrin, they are like each other and like gelatin in being newly formed protein threads. They also shrink, that is shorten, after they have been formed—hence an old scar is usually sunken and somewhat puckered.

INTERNAL REGULATION AT WORK

RAPID ADJUSTMENTS—NEURAL. Now that we have looked at some of the most important blood attributes which are kept constant and the homeostatic mechanisms which keep them so, we can at last see how some of these work together in the actual functioning of the body. Let us return to where this book started and see what adjustments the body makes in the relatively simple change from rest to strong exercise. An animal, or man, really goes “all out” only when

he faces a general emergency. Except for some human emergencies which depend on special social situations, such as winning for Home College, most of these crucial times are likely to be matters of life or death. In either case, an intense emotion is set up and, under the whipping of stark fear or anger, intense danger or excitement, man and animals alike are able to perform feats of strength, speed, and endurance which are far in excess of their normal working capacities.

Whatever the immediate stimulus—an enemy or an automobile bearing down upon one—impulses reach the nervous system and act especially upon the hypothalamus. This integrating center of the autonomic nervous system is stirred up and broadcasts a body-wide alarm to the periphery. The orthosympathetic nerves discharge sympathin at all their effectors; to a lesser extent the parasympathetic nerves may increase their action. Among the orthosympathetic effectors reached is the adrenal medulla, which responds by releasing large amounts of adrenalin into the blood to reinforce the sympathin. At the same time, motor pathways in the central nervous system and peripheral motor nerves are busy ticking out their properly timed and directed Morse code messages to the skeletal muscles; and these, nearly all in the body, are frantically contracting and relaxing—in the coordinated manner dictated by the nerve impulses—to send the body bounding along the ground. During such violent exercise, the total body metabolism is increased many times, sugar and oxygen are taken from the blood in greatly increased quantities, much heat is generated, and the arteriolar and capillary flood gates in the whole muscular system are thrown wide open to let the necessary blood gush past the avid cells.

Emergency and self-preservation. Now see how it all fits together. The action of the orthosympathetic nerves, supplemented by the hormone, adrenalin, causes a breakdown of liver glycogen and the pouring out of glucose into the blood. They greatly multiply the cardiac output, but inhibit the activity of the temporarily unimportant intestine. The arterioles through the body tend to constrict, but the local production of carbon

dioxide overcomes this action in the busily working muscles and their vessels remain open. The great vascular bed in the viscera, however, squeezes down and forces its blood back to the heart. An organ not yet mentioned, the spleen, a spongy sac of very loose tissue filled with fluid blood and extra blood cells and surrounded by a capsule of muscle, also contracts and squeezes into circulation the reserve of blood held by it. With the visceral vessels clamped shut and those of skeletal muscle widely opened, practically the entire blood of the body is kept boiling around from heart to nervous system and muscles, to heart, to lungs, back to heart, and so around again, at a greatly increased rate and with the temporarily unused organs left almost bloodless and inert. The great excess of carbon dioxide rushing out of the muscles acts upon receptors, in the lungs and in the carotid body, which reflexly stimulate the respiratory center, and also directly on this center itself; so that breathing movements are increased and bring in oxygen as rapidly as it is being used.

At the height of such a burst of activity, 40 liters of air pass in and out of the lungs per minute, as compared with 7 at rest; 4 liters of oxygen are taken up from the blood and used as compared with 0.3; the heart pumps 30 liters of blood per minute instead of 4; the time taken for the average drop of blood to get around the body is decreased from 20 seconds to 10 or less; and the muscles increase their normal rate of energy production, 3 calories per 100 grams per minute, to 150. The extra oxygen used by the muscles, to burn glucose, would yield only 60 calories per 100 grams per minute so that the remaining 90 calories increase is obtained by the formation of lactic acid. This finally exhausts the alkaline reserve and develops a great oxygen debt. Many other lesser adjustments are made by the body at this time, of which only some can be mentioned: The blood becomes more coagulable, that is, its clotting time is shortened; the pupil of the eye dilates and lets in more light; the action of adrenalin and the orthosympathetic nerves on skeletal muscle itself produces chemical changes in the muscle fibers which decrease their fatigue or slow the

rate at which fatigue develops; there are shifts of salts, acid, and water between tissues and blood; and so on.

You will note that practically every change is such as to help along the immediate crucial need for maximal maintained muscular effort. Only in the matter of heat loss is there some discrepancy, for decreased blood to the skin and erection of hairs hinder rather than help this; but even a decreased heat loss is perhaps useful for a while for, as body temperature rises, the speed of action of all its cells, including the all-important muscle, is enhanced, and the animal can actually run faster than if it did not get heated up. Another body change related to emotion, although not necessarily to exercise as such, is the tendency to evacuate the rectum and bladder, and both these responses depend more on the action of parasympathetic than of orthosympathetic nerves. It may perhaps be useful in an emergency to drop ballast rather than to carry it along.

SLOW ADJUSTMENTS—HUMORAL. The example just developed is one of rapid adjustment and it is not surprising that the mechanisms used in achieving it are overwhelmingly neural. By way of contrast, we will consider one of the slow bodily adjustments, as important for race preservation as are the emergency ones for self-preservation, that of the menstrual cycle. This, as anticipated, is preponderantly under the control of the more slowly acting endocrine glands and hormones.

Menstruation. Let us start with a young girl before puberty, whose still infantile vagina leads to a similarly underdeveloped uterus from which, in turn, the two oviducts open into the pelvis with an ovary loosely cupped in the end of each. The ova are all immature, no properly developed egg has yet been formed, and the girl has never menstruated. Then, at about thirteen years of age, the situation changes in the course of a few months; the breasts swell, the development of vagina and uterus is completed, and ova begin to mature. An egg enlarges, becomes surrounded with layers of special ovarian

cells with fluid between them, and the whole structure protrudes from the ovary's surface like a blister. This follicle finally ruptures, the egg drops into the oviduct, and is gently passed into the uterus by the beating cilia of this tube; and there, since no sperms are present to fertilize it, it dies.

A fortnight later the first menstruation occurs; and from then on the cycle of ovulation and menstruation recurs at ap-

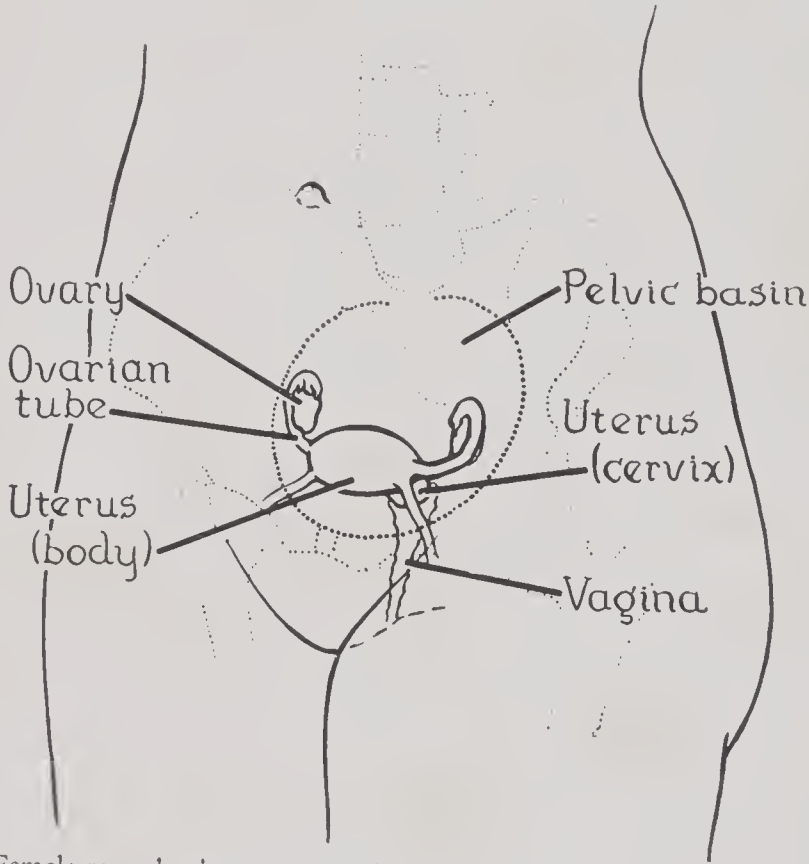


FIG. 40. Female reproductive system. The two unlabeled bands running forward and downward from the body of the uterus are supporting ligaments which help to hold it in proper position. (Drawn by E. M.)

proximately monthly intervals (menses means literally monthlies), except as interrupted by pregnancy or disturbed by disease, for some three or four decades, until the menopause. In human beings, nerves have little or nothing to do with these complex changes. (This is not true for all animals. The rabbit, for example, ovulates only after coitus or other mechanical stimulation of the vagina, acting in part through the nervous system.) The ovary, removed from its normal position and replaced elsewhere in the body, or a bit of uterus implanted into the eye

where it can be watched through the transparent cornea, continues to go through its normal cycle of variations, though lacking now any possibility of nervous control.

Biological rhythms. Here is an example of an extremely interesting biological phenomenon; a repeated rhythm which is, obviously, under some sort of regulation. The questions at once arise: Is the control itself rhythmic, and, if so, what determines the rhythm of the control, and what the rhythm which guides that one; or, if somewhere along the line a constant control is operating, how does it bring about rhythmic changes? Have you ever thought about why a flag flaps in the wind instead of standing straight out? And have you noticed that, the more steady the blow, the more continuous and regular is the rhythm of the flag? The high-frequency note of a violin string stays regular only while the bow is drawn continuously and steadily across it; the unvarying alternation of day and night results from the constant rotation of the earth; and, in general, regular rhythmic changes always turn out to depend finally upon some constant driving mechanism. There are many biological rhythms—the annual one between hibernation and activity of many mammals; the sex rhythm, repeated at intervals of about five days to fifty weeks in different species; the daily rhythm of wake and sleep; the faster ones of respiration and the heart beat; the still faster electrical rhythms of nerve cells; and the high-frequency rhythmic discharges, up to 500 or even 1000 a second, set up in nerve fibers by receptors.

One pituitary hormone. So, underlying the menstrual cycle (or estrus cycle as it is more generally called, to include the equivalent changes of “heat” or “rut” in animals which do not actually bleed from the uterus) there must be some fundamentally constant governor which comes into activity at puberty and continues until change of life. This factor is the hypophysis, though it acts through fluctuating secretions, for the gland reaches its functional maturity late in adolescence, probably by intrinsic growth. If the pituitary is diseased or removed, the body remains sexually immature through life; in-

cidentally, the male equally with the female. The mature hypophysis, then, begins to secrete a hormone which leads to the development of the sex organs, and continues to secrete this till old age—except as other hormones act upon the gland to increase or decrease its hormone production.

It is simple to show, by removing the ovaries, that this pituitary hormone acts upon them only; for in their absence none of the other puberty changes occurs. We have now the first links in the sequence—the developed hypophysis secretes a hormone which stimulates the ova to develop and the follicles to form; and the ovary with ripening follicles, but not the one without them, produces another hormone which is necessary to bring about the changes in the uterus and mammary glands. Actually these substances have been purified and even the amounts lost daily in the urine, and sometimes those present in the blood, have been determined. Let us call the hypophyseal substance the follicle-stimulating hormone and that produced by the follicle, estrin (a substance necessary to estrus).

Visible sex changes. Now we had best glance at the actual changes occurring through the menstrual cycle. At the end of the few days of bleeding, the mucous membrane of the uterus is thin and inactive. During the following week, this lining slowly thickens, partly by an increase in its cells, partly by an increase in the quantity of blood contained in its vessels. Through another week, these changes continue and, in addition, the glands buried in the wall of the mucosa become active and swollen with a thick sticky secretion. This is the time when the ovum normally reaches the uterus and, if fertilized, will become implanted in the mucosa. The uterus is thus prepared to receive the new embryo and nourish it through its ensuing development into a fetus. In the usual absence of a fertilized egg, however, the mucosal secretion diminishes and, after another ten days, the surface of the swollen mucous membrane comes away, along with blood from the vessels thus opened, and menstruation is initiated. By the time the discharge is over, in four or five days, the mucosa is healed, shrunken, and ready

to begin again its next preparation for a house guest. Less striking, but easily recognized and equally consistent, changes occur in the lining of the vagina; so that it is possible to tell, from the appearance of cells swabbed from it day by day, in just what stage of a cycle a woman is.

In the ovary, itself, the most striking landmark of activity is the actual ovulation, the discharge of the ripe egg. This

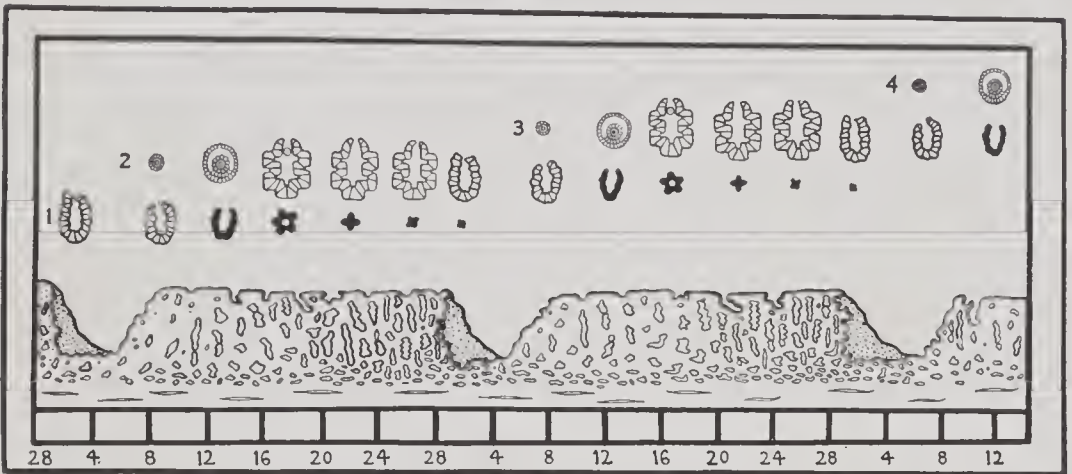


FIG. 41. Diagram of the structural changes in the uterine mucous membrane (below) and in a single egg follicle in the ovary (above) over a period of slightly more than two complete menstrual cycles. Days since the beginning of a menstruation are shown at the bottom, the bleeding uterine mucosa being indicated by the stippled area. The thickness of the mucosa is roughly diagrammed and the considerable decrease in its thickness during menstruation is apparent. The state of the uterine glands is also to be noted. Above are shown changes in four follicles, in the order in which they develop at successive menstruations, from below to above. Only one sequence (2) is complete. In this, the unripe follicle is first shown eight days after the first menstruation. It develops progressively and ruptures—that is, ovulation occurs—about two weeks after the start of menstruation. Then the remaining follicle cells develop into the corpus luteum, which slowly shrivels and disappears during the succeeding menstrual cycle. (Modified from Bailey, *Textbook of Histology*, drawn by P. McC.)

does not occur at the time of menstruation but commonly twelve to thirteen days after the beginning of the previous menstrual period; that is, almost half way between successive menstruations. Since it may take two days to a week for the ovum to travel to the uterus, it thus arrives just when the uterine mucosa is nicely prepared for it. But what happens to the rest of the ovarian follicle after it has ruptured and lost its egg? A small blood clot forms and is soon penetrated by cells from the follicle walls to produce a solid cell mass, which remains

as a small bump on the ovary's surface. The original follicular cells do not merely grow to fill the clotted cavity but they change their nature as well, for the solid body formed has a distinct yellow color; hence its name, corpus luteum.

Ovarian hormones. The corpus luteum, then, forms after ovulation, about a week after the close of menstruation; and it continues to grow for another week, while the uterine glands are increasing their secretion. If a fertilized ovum is present, and pregnancy develops, the corpus luteum remains, as does the thickened and secreting uterine mucosa; but in the absence of pregnancy, the corpus luteum, again like the uterine mucosa, decreases during the next ten days and is gone by the time menstruation starts. This close parallelism between the size of the corpus luteum and the behavior of the uterine mucosa, especially the activity of its glands, suggests that a hormone from the corpus luteum controls these changes in the uterus which prepare it for pregnancy, or gestation. This hormone also is known, and appropriately called progesterin.

When progesterin is injected into an animal, the uterus of which is in the proper state, it brings on the expected mucosal changes. Conversely, if the corpus luteum is removed when the uterine mucosa is swollen, menstruation promptly occurs and the mucosa lapses back to its resting state. The same is true even during early pregnancy, for removal of the corpus luteum leads to rapid abortion. Fortunately this works in reverse as well, and it is often possible to prevent abortion or premature delivery by continued injections of progesterin. (Actually the situation is more complicated for, during the last half or third of pregnancy, the corpus luteum can be removed without serious consequences and without diminishing the amount of progesterin derivative appearing in the urine. Some other tissue, apparently, takes over the formation of this substance towards the end of pregnancy, and suddenly stops producing it at term, when the baby is delivered. The placenta is the probable source.)

But is there not a gap in our explanation? The uterine mucosa starts growing a day or two after menstruation is over

but the corpus luteum and its progestin are not present until a week later. Some other hormone must be responsible for this earlier development; and, since the changes involved are similar to those which transform the immature into the mature organ, we would naturally suspect our previously discovered substance, estrin. This has been duly established.

The position now is this: the follicle in the ovary ripens and produces estrin during about the first half of the intermenstrual period, and this hormone causes the first growth of the uterine mucosa (proliferative phase). Then ovulation occurs, the corpus luteum forms, the changed cells secrete a different hormone, progestin, and this completes the changes in the uterus (secretory phase) preparatory to receiving the egg which is traveling towards it. (Incidentally, these same two hormones contribute to the development of the breasts, although they probably act indirectly by stimulating the formation of one pituitary hormone and inhibiting that of another. It is the second of these which finally causes milk to flow after the child and placenta—with its inhibiting progesterone—have been delivered.)

The hormone machinery. At last we are ready to look into the control of this rhythmical ovarian hormone machinery. We have seen that a follicle-stimulating hormone from the pituitary is necessary to have the follicle develop and produce estrin. Perhaps we are not surprised to find that a second pituitary hormone, the luteinizing hormone, is the means of changing the follicle cells into a corpus luteum and making them secrete progestin. This may seem complicated, but it is none the less the case; for removing the hypophysis after the follicle is ripe, or even ruptured, prevents the development of a corpus luteum. We might have expected the original follicle-stimulating hormone to do this job also, but the two substances do exist. The hormone which grows the follicle has been separated from that which luteinizes it. So now we have to account for the cyclic changes in these two ovary-stimulating pituitary hormones.

Starting again at the time of menstruation, first the follicle-stimulating and later the luteinizing hormone are poured into

the blood in increasing amounts until, rather abruptly, just before the next menstruation begins, they drop back to their initial low level. We have seen over and over again how a stimulus leads to the kind of response which will stop that stimulus; for example, the stretch of the carotid sinus receptors by high blood pressure leads to responses which lower blood pressure. Would a similar situation help here? Suppose one or both of the ovarian hormones, carried by the blood to the pituitary gland, can suppress its activity in secreting one or both of its ovary-stimulating hormones. A rhythm would automatically result.

The adult hypophysis is geared to secrete its hormones continuously, but towards the end of a menstrual cycle the large quantities of ovarian hormone (probably mainly estrin) have inhibited it, so that little or no hypophyseal secretion is occurring. In the absence of the necessary pituitary hormones, ovarian activity gives out and the progestin in the blood rapidly falls. The uterus, of course, responds by menstruation, and at the same time the inhibition of the hypophysis is removed and it progressively resumes its active secretion of the ovary-stimulating hormones. The ovarian hormones then steadily increase, the hypophysis is again inhibited, and we are around the cycle and ready for another whirl.

I have purposefully been a little vague in saying which of the ovarian hormones acts upon the hypophysis or what is the exact sequence of interaction between the two pituitary and the two ovarian substances—for the excellent reason that we are still far from certain of these points. In fact, there is even reason to think that estrin may at first stimulate the hypophysis and only secondarily decrease its activity by “exhausting” it. But in spite of some uncertainties, far more is known and far greater complexities exist than we have taken into account. The important influence of these sex hormones on mating and maternal habits, on emotional states, even on dream content, for example, are being rapidly unraveled. And one final point, lest some of you should feel neglected; both the female hormones secreted by the ovary and the male hormones secreted by the

testes are present in men and women alike. Women have somewhat more of the former, men of the latter, and these various hormones (chemically extremely similar to one another) actually perform important duties in both the male and female body. Also, you might profitably think about how the presence of a fertilized egg causes the corpus luteum to remain intact and stops the menstrual cycle.

The hypophysis acts as over-lord of all the sex glands and indeed of all the endocrine glands except, perhaps, those necessary to life itself; for other hormones from it are similarly necessary, for example, to maintain the activity of the thyroid and of the adrenal cortex. It is especially interesting, therefore, that the hypophysis is so closely associated with the central nervous system and is actually formed in part by an outgrowth from the embryonic brain.

So there is your body, shot through with telegraph and transport systems, with nervous and hormonal mechanisms, which stimulate and inhibit effectors, which interact with each other, wheels upon wheels which keep your vital machinery running smoothly day after day and year upon year with no conscious attention, whether you know about it or not, and with an amazing record of continuous performance without breakdown or repairs. Again, don't you think you have something to be proud of?

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PART II

CHAPTER VI

CIRCULATION

THE VASCULAR SYSTEM. The circulatory system has a simple duty and discharges it in a fundamentally simple way. The blood and, less, the lymph and other body fluids must be kept moving past the cells in various organs, to maintain their "internal environment" constant despite the continuous changes of metabolism.

General plan. The blood is moved by a force pump through pipes, many of which can change diameter and, acting as valves, control the flow. Half the circulation might be compared to a city water-supply system: From an essentially unlimited reservoir, water is pumped into the central mains under pressure; it flows through ever smaller conduits to reach individual buildings; and finally particular faucets are turned on and off in accordance with local needs. The water actually functions only as it leaves the faucets; the preceding system serves merely to guarantee delivery at an adequate and reasonably constant pressure. The heart is the pump, the arteries and fine arterioles are the conduit system, and the faucets are the capillaries; and it is only the flow of blood through each capillary in accordance with local cell needs which is important. Further, the number of capillaries per gram of tissue is related to its metabolic needs.

From here on the circulation must be compared rather with the sewage-disposal system. The waste water collected from the sinks, etc., moves, under no pressure but its own weight, through ever-larger joining conduits until it passes through a purification plant and is discharged. Since the waste

water flows under very low pressure, the conduits are of proportionately greater caliber than are those bringing in the fresh water—contrast the half-inch pipe connected to the faucet with the two- or three-inch one from the drain.

In the body, the capillaries pass continuously into venules, small and large veins, and through purifying organs, as liver, lungs, and kidneys. (In some organs, as liver and spleen, there are hardly true capillary channels between arterioles and venules but rather open spaces or sinusoids in the spongy tissue mass. These correspond more closely to the open system between faucet and sink.) Here the essential difference between the systems we are comparing shows up: Blood is far too elaborate and precious to be used once and thrown away; relatively small amounts of liquid must circulate over and over again and must, therefore, be restored carefully to the original condition.

The most urgent requirement of cells is the continuous supply of oxygen and removal of carbon dioxide, and there is little leeway in the amounts of these substances which must be present. It is not surprising, then, that *all* the venous blood is passed from the heart through the lungs, where these gases are brought back to the desired concentrations, before again going to the body. On the other hand, much but not all venous blood passes through an extra set of capillaries in the liver before reaching the heart; and only a fraction of the arterial blood passes through the kidneys on each round trip. These organs help control the supply of foodstuffs and the removal of wastes and, as long as they act rapidly enough to keep the average blood composition constant, it is unimportant when a given bit of blood passes through them.

The heart can pump the blood separately through lungs and body because it is a double pump. The great veins empty blood returning from the body into the right half of the heart—into the auricle and then into the ventricle—which pumps it along the pulmonary artery to the lungs. There the vessels change from arteries to capillaries and the blood from “venous” to “arterial,” and veins pour the freshened blood into the

left auricle of the heart. The left ventricle is built like the right but with thicker walls, which makes it a stronger pump. (The aortic blood pressure is correspondingly higher than the pulmonic.) From the left ventricle, the arterial blood enters the great aorta whose branches distribute it to all organs of the body—including the walls of the heart itself. You will do well to study Fig. 37, which diagrams the more important pathways of the blood.

Lining. The narrower arteries, which carry blood rapidly under high pressure, have thick walls; the wider veins, through

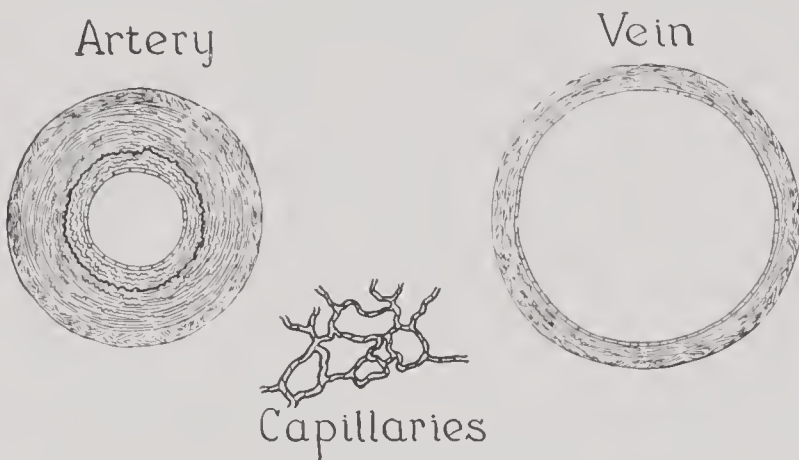


FIG. 42. A single layer of flat endothelial cells constitutes the entire capillary wall and the lining of arteries and veins. The two latter have, in addition, smooth muscle and elastic and non-elastic connective tissue cells and fibers in their walls. The relatively thin-walled veins have little elastic tissue. The heavy-walled large arteries have little muscle but a rich supply of elastic tissue, part of which is condensed into a practically continuous elastic layer, shown by the heavy black line. (Drawn by E. M.)

which blood flows sluggishly under low pressure, have thin ones, composed of inert fibrous tissue with some admixed smooth muscle fibers. But both are alike lined with a continuous layer of beautifully smooth and flat endothelial cells, a layer which extends throughout the vascular system, including the heart, and, like the smooth and clean surface we studied in connection with coagulation, it helps keep the blood from clotting.

When the lining is injured—by wound, infection, or chronic disease—small clots form on the damaged walls. These thrombi may grow to occlude the entire vessel and may even

break loose (then called an embolus) and be lodged in some smaller vessel. The effects of the thrombus will depend, of course, on the vessel obstructed—a sudden paralytic stroke when the blood supply to part of the brain is stopped; an acute heart attack, perhaps death, when a branch of the coronary artery is plugged and the heart muscle deprived of

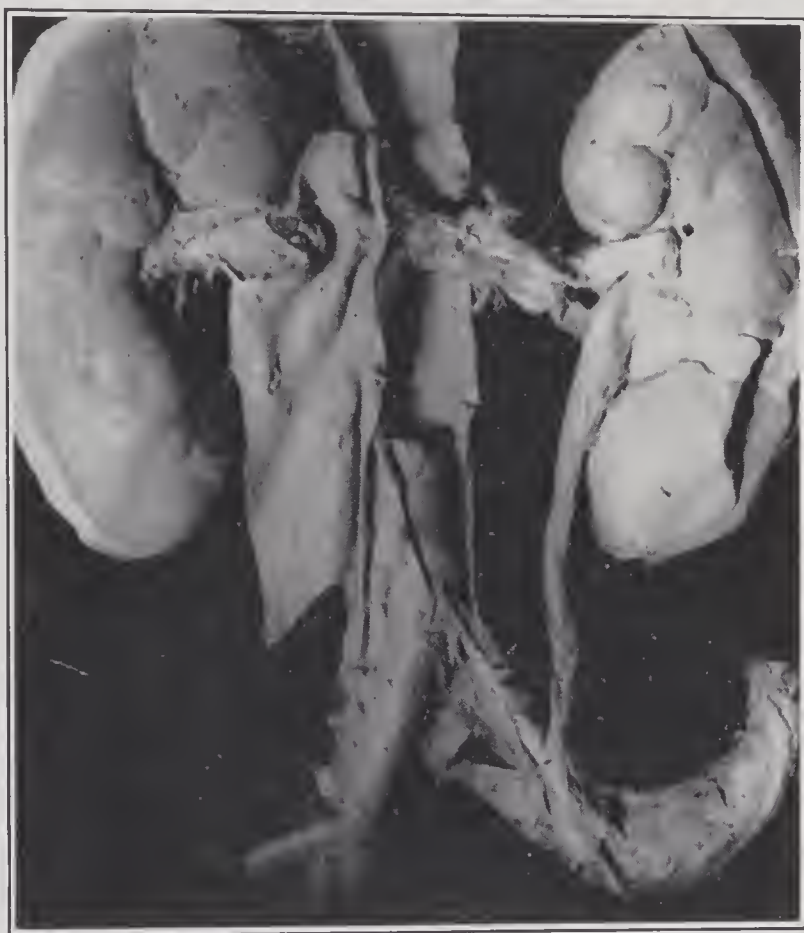


FIG. 43. This pathological specimen of the lower aorta, sending branches to the two kidneys and then dividing into the two main leg arteries, shows a large thrombus completely occluding its lower portion and others extending into the renal arteries.

blood; death of tissue masses and gangrene when the circulation in a limb or an internal organ is blocked.*

The capillaries, which must permit maximal exchange of substances through their walls, possess practically no structures other than this thin endothelium with an occasional isolated

* Can you reason out from the location of the clot, in artery or vein, whether the gangrene will be dry, so that the tissues shrivel up, or wet, owing to edema?

contractile cell upon its surface. The heart is a wall of almost pure muscle covered on the outer as well as the inner surface with slippery endothelium. The outer membrane is doubled back on itself so that the heart hangs practically free in a sac. Since the heart's duty is mechanical pumping, its muscular wall is understandable and so is its "oiled" outer surface which permits it to slip to and fro. The inner endothelium of the heart is especially elaborated into pleat-like folds which, with

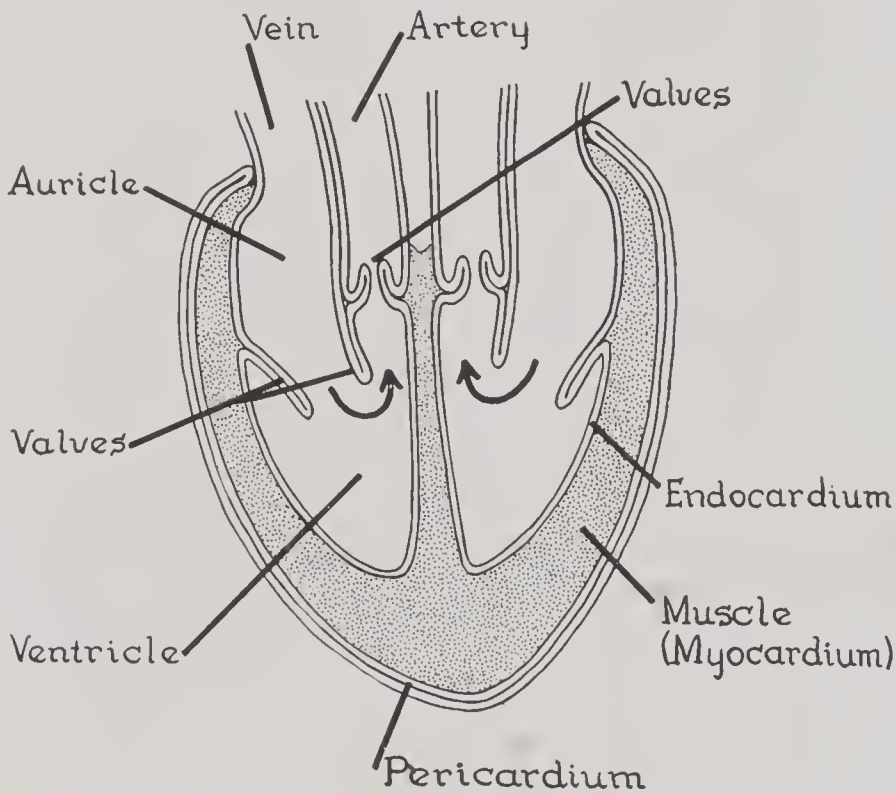


FIG. 44. The endothelial lining of the vascular system continues as the lining of the heart chambers (endocardium) and covers the heart valves. A similar endothelial layer (the pericardium) covers the cardiac muscle on the outside and is folded back upon itself to make a closed sac in which the heart can move freely. (Drawn by E. M.)

fibrous tissue between the layers, form four sets of valves; one set on each side between auricle and ventricle and one between ventricle and artery (Fig. 44).

Arteries. The thick arterial walls are tough for, throughout life and with no release, they must resist the high pressure of the blood within them; and elastic, so that the vessels can pulsate, since new blood is forced in suddenly and intermittently by the heart, while that already present leaks through

their open ends into the capillaries more slowly and continuously. The main thickness, therefore, is not made up of the smooth muscle present but of practically continuous sheets of interwoven fibers of elastic connective tissue. The arterial wall is not unlike a stretched rubber sausage-shaped balloon. When blood pressure falls to zero at death the arteries promptly

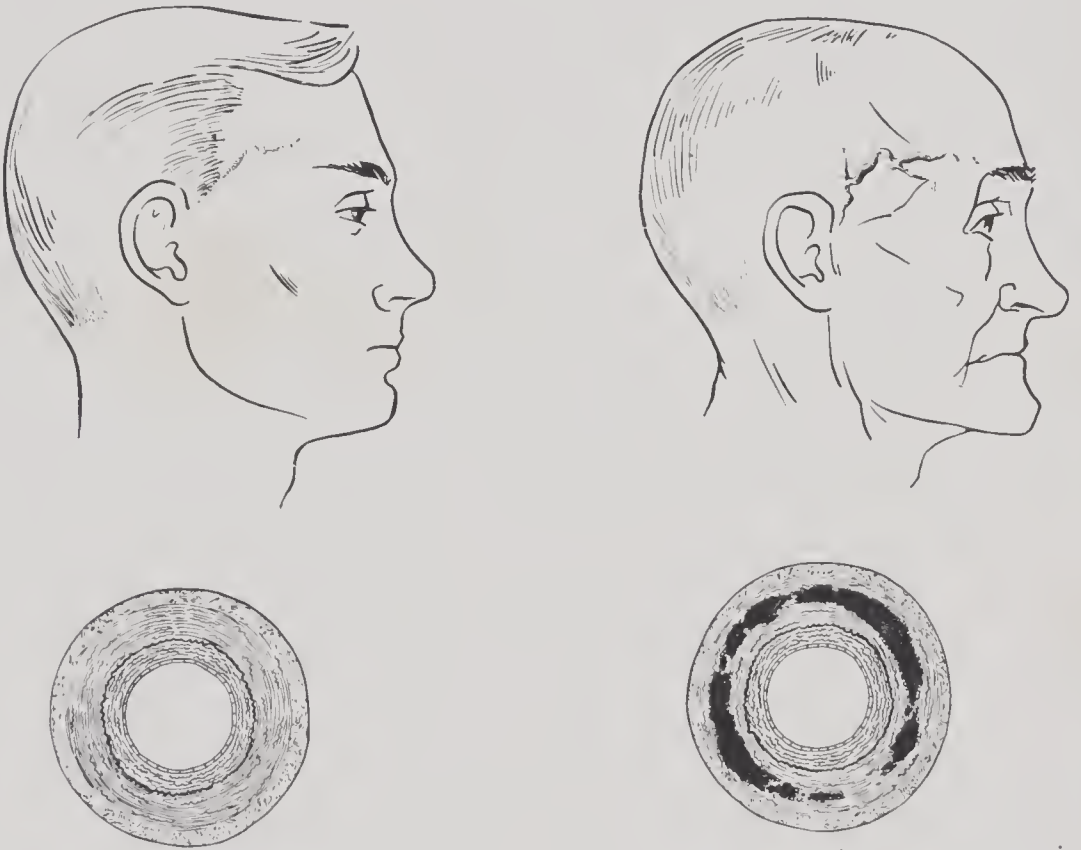


FIG. 45. The normal, straight, soft-walled temporal artery of a young man is hardly visible below the skin of the temple. In an old man with sclerosis, the vessel wall is hardened by calcium deposits and the tortuous artery is clearly visible and can be felt through the skin as a hard "pipe stem." Below are shown cross sections of the normal and sclerotic vessels. The black masses indicate calcium granules. (Drawn by E. M.)

collapse, like the punctured balloon. (It was, in fact, because the ancients found the arteries of cadavers empty or apparently containing air that these vessels bear their name. Artery means air tube.)

With advancing age, the elastic arterial walls, again like rubber, tend to harden and lose their extensibility. Moderate arteriosclerosis is normal with aging, but in certain diseases the hardening is excessive and premature and it results in-

evitably in higher blood pressure, since the walls no longer yield properly each time the heart pumps in more blood. Sooner or later, as the walls become more brittle and the pressure within them greater, an artery gives way somewhere, most frequently in the brain—another important cause of sudden stroke or death.

Veins. Most veins possess valves, resembling those of the heart but more delicate; only those large veins running up the trunk to the heart and from the head down to it lack them. Remember that blood enters the veins, say in the foot, under

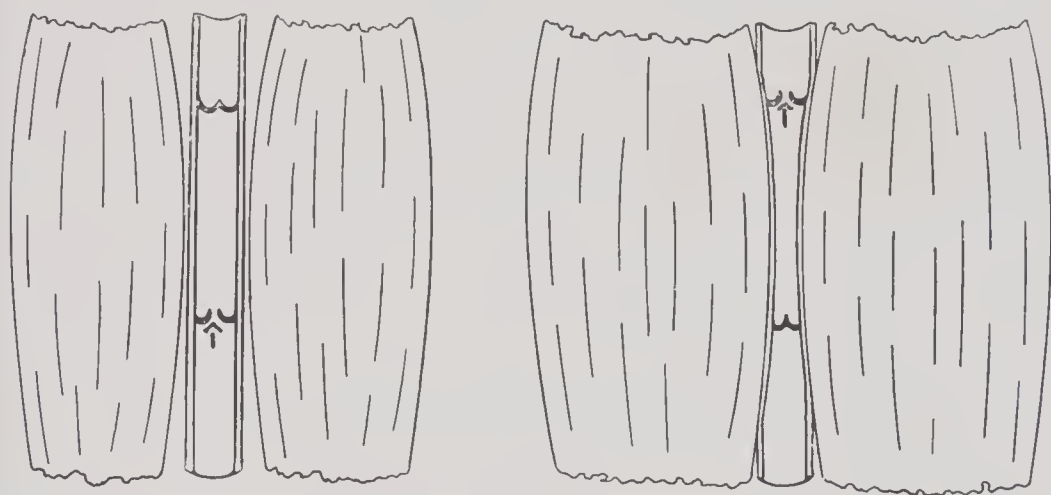


FIG. 46. A vein ascending in the leg between muscles is "milked" by the muscle movements. At the left the muscles are shown relaxed with blood moving up through the open lower valves into the section of vein newly released from muscle pressure. The upper valves are closed, preventing the backward flow of the blood from above. On the right the muscles are contracting and compressing the vein. The lower valves are closed by this pressure, this prevents any backflow, and the blood is therefore pushed upwards and opens the valves above. (Drawn by P. McC.)

low pressure and must somehow be lifted against gravity. If they had no valves the whole weight of a column of blood some four feet high would push backwards against the oncoming blood in the foot and seriously impede the circulation. Of course the mere existence of valves would not help if the veins were rigid tubes, for the whole column would still have to be pushed up from below. Actually, veins run among the large skeletal muscles, which continuously change their shape during ordinary activity and so irregularly squeeze and release the pliable vessels. When a contracting muscle com-

presses a vein the valves below stay shut, those above open; and when the vein is released again the upper valves close and hold up the blood column while the lower ones open to allow the vessel to refill from below.

This mild pumping or "milking" action by muscle is very helpful; its relative absence during standing for long hours makes this more fatiguing than walking about. You can easily demonstrate that even the muscle contractions during standing help the leg circulation. Remove both shoes and stand for several minutes on one foot on a stool high enough so that the other foot, left hanging limply over the edge, does not quite touch the floor. After, say, five minutes of quiet standing try to put your shoes on. The shoe will slip onto the foot of the supporting leg, whose muscles were actively contracting; but the foot of the leg which hung relaxed will be so swollen that the shoe may not go on. In the latter, the blood had to push from the capillaries into the venules against the weight of the whole venous column, and an increased capillary pressure resulted. This led to a greater filtering out of blood fluid through the permeable capillary walls and so to a mild, temporary edema.

One last point. Obviously this problem arises only with veins carrying blood against gravity—while we lie in bed with our muscles relaxed, no edema of the legs develops. Now why should the great veins, lifting blood from our hips to our heart, not be supplied with valves like those bringing it from the toes to the hips? Can you think of an answer? Certainly such valves would be useful; the frequent occurrence of varicose veins in the leg—especially in women who stand long hours at their work—attests that the venous circulation in human legs is not what it should be and is precariously near the danger point of malfunction. Valves in the great abdominal and thoracic veins would indeed help man, who carries his trunk erect; but, you see, they would be quite unnecessary to a four-footed animal whose trunk is horizontal. Man has achieved his upright position but has not yet evolved the valves in the veins that should accompany it. Actually, many human struc-

tures have not changed as would be needed to adapt man to his recent habit of walking erect, and so constitute additional bits of evidence of the evolution of man from a quadrupedal ancestor.

PROOF THAT THE BLOOD CIRCULATES. The presence of valves, in other veins, afforded one of the arguments marshaled by William Harvey three centuries ago to prove the circulation of the blood. You may perhaps think it strange that someone had to "prove" the circulation of the blood. Yet the greatest scientists and doctors of earlier times—Hippocrates, Aristotle, Galen—and for two thousand years, remained convinced that the blood does not circulate. The capillaries were unknown to them, since they had no microscopes; and the arteries, we have seen, they believed to be filled with air, a special gaseous "spirit." The blood was, therefore, restricted to the veins, in which it flowed and ebbed, forward and backward, as the heart squeezed out its contents or relaxed to let them flood in again. The valves and midwall of the heart were "explained" by invisible channels which let the blood past.

If any one achievement stands out as initiating modern biology, it is that of Harvey in proving that the blood does circulate. (You will be surprised what good reading his book, *On the Motion of the Heart and Blood*, published in 1626, still makes; try it.) It was epochal because it brushed away not merely the erroneous beliefs about the blood, but the whole set of elaborate, fantastic, and completely futile notions about "spirits" or "humors" which constituted the biological dogmas of the day. Its dramatic effect on man's thought was comparable to that of the demonstration by Copernicus that the earth moves around the sun rather than the reverse; and it was likewise resisted furiously—as are all great new discoveries which revolutionize our beliefs. And Harvey's conclusion, as that of Copernicus, gained acceptance nonetheless, by the sheer logical force of the experiments supporting it—the proper procedure of science.

Harvey showed, for example, that blood spurted only from that end of a cut artery connected with the heart but not from the other, while with a vein blood welled out, not from the central end opening to the heart, but from the peripheral end alone. He emphasized the significance of the valves and proved by magnificently simple experiments, which you can now do on your own hand, that these valves do prevent a backward flow of blood in the veins. Let your hand lie limply on your lap for a moment and then select a nicely bulging superficial vein in the skin on its back. Rub your finger along the vein in the direction from knuckles towards wrist, and note that, although the vein collapses under the finger, it refills from the periphery behind the moving finger. This can be continued for hours, with no chance for blood to run peripherally in the vein, until more blood than the body contains can be "milked" towards the heart. Now stroke in the opposite direction and note that the vein remains empty behind the finger, below some point at which a valve holds back the blood above it. As the finger continues, peripherally, the vein quite suddenly refills, from below upwards, when the compression has passed a point where a second vessel happens to join the one being studied.* There is just one conclusion possible from these simple experiments, in plain view of the unseeing eyes of ordinary man: Blood is continuously delivered along some other channel to the peripheral end of the vein and flows back along the vein to the heart; in other words, the blood circulates.

THE HEART. Though valves in the veins are useful, those in the heart are absolutely essential. Their action is nicely timed with that of the muscle in a regularly repeated cycle.

The cardiac cycle. When the heart is quietly relaxed, during the brief pause after diastole, blood steadily accumulates in

* Can you think of reasons why there should be no valves in the arteries; and why arteries of any magnitude are buried deep in the flesh, although relatively large veins are freely present in the skin and at other superficial positions?

the right auricle from the vena cava and in the left one from the pulmonary veins; and some passes through the open valves between relaxed auricles and relaxed ventricles and enters the ventricle of each side. The next heart beat is initiated by the simultaneous contraction of the two auricles with the ventricles still relaxed. There are no true valves between auricles and veins but they connect at a sharp angle so that the thin auricle

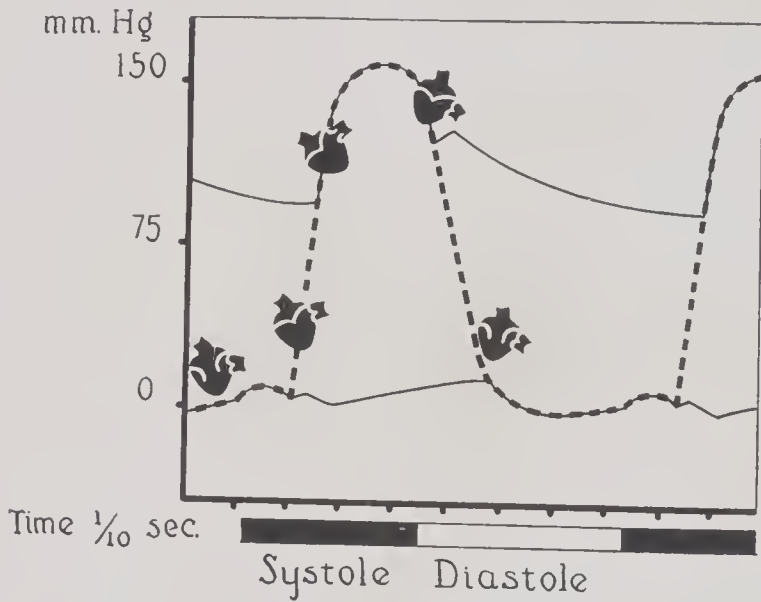


FIG. 47. In this graph, pressures in millimeters of mercury are indicated in the left margin, time in tenths of a second is shown below. The three curves represent the blood pressures within the left auricle (lower solid line) and the left ventricle (heavy dotted line) and the aorta (upper solid line), as these pressures vary through the course of a heartbeat. Obviously, during the times when the pressure in auricle and ventricle is the same, the auricular-ventricular valves must be open; when these pressures are different the valves must be shut. In the same way, the ventricular-aortic valves must be open while the ventricular and aortic pressures are alike. The valve positions are indicated in the little inset diagrams above the points where they change position. (Drawn by E. M.)

wall forms a flap which serves partly as one. Some blood does, however, squeeze back into the veins, so that those near the heart pulsate feebly. You have certainly observed the rhythmical swelling and emptying of neck veins, especially in an excited person. But nearly all the blood in the auricle is simply pushed on into the relaxed ventricle, a cavity at practically zero pressure ready to receive it. This completes the “priming” of the pump.

Just after the auricular systole, the ventricle begins its sharp powerful contraction. The pressure within it immediately increases and promptly slaps shut the auriculo-ventricular valves. Since the auricles are already relaxing and are weak thin-walled sacs at best, these sturdy A-V valves alone keep the ventricular contents from flooding backwards. The only exit from each ventricle, then, is through the ventriculo-arterial valves into the aorta or the pulmonary artery. But the arterial pressures, though now minimal, are still far above those in the relaxed ventricles; so while ventricular systole is gaining momentum, while the cardiac muscle is developing tension, no blood leaves and the muscle is contracting isometrically. The intraventricular pressure rises precipitously, as fast as muscle tension develops, and in some five-hundredths of a second it has reached and exceeded the pressure in the artery, about 80 millimeters of mercury in the aorta.*

The aortic valves now open, the ventricular blood is ejected rapidly; the elastic walls of the artery are further stretched; and the pressure in ventricle and aorta, for the moment freely opening into each other, continues to rise to 120 millimeters. The ventricle has now shot its bolt and begins to relax. Blood starts to flow backwards from the aorta, but the first slight movement in this direction snaps shut the aortic valves and prevents this regurgitation. The ventricle finishes its diastolic relaxation and the pressure in its cavity drops abruptly, soon falling below that in the auricle, which has received a steady flow of venous blood ever since its own diastole. The A-V valves now open, of course, and the venous blood continues to

* Blood pressure, however measured, is expressed as a pressure exerted by a column of mercury. The atmosphere will hold up (in a vacuum) a column of mercury 760 millimeters high; hence atmospheric pressure is 760 millimeters of mercury. An additional pressure of 80 to 120 millimeters of mercury must be applied to the outside of an artery to make it collapse against its internal blood pressure. An air-tight bag is wrapped around the arm and inflated until the pulse can no longer be felt in the wrist (or heard in the elbow hollow). The pressure in the bag, then equal to systolic blood pressure, is measured by a manometer. Diastolic pressure is determined similarly. In animals, the opened artery is often connected to a manometer by a tube filled with salt solution and the pressure in it is directly measured.

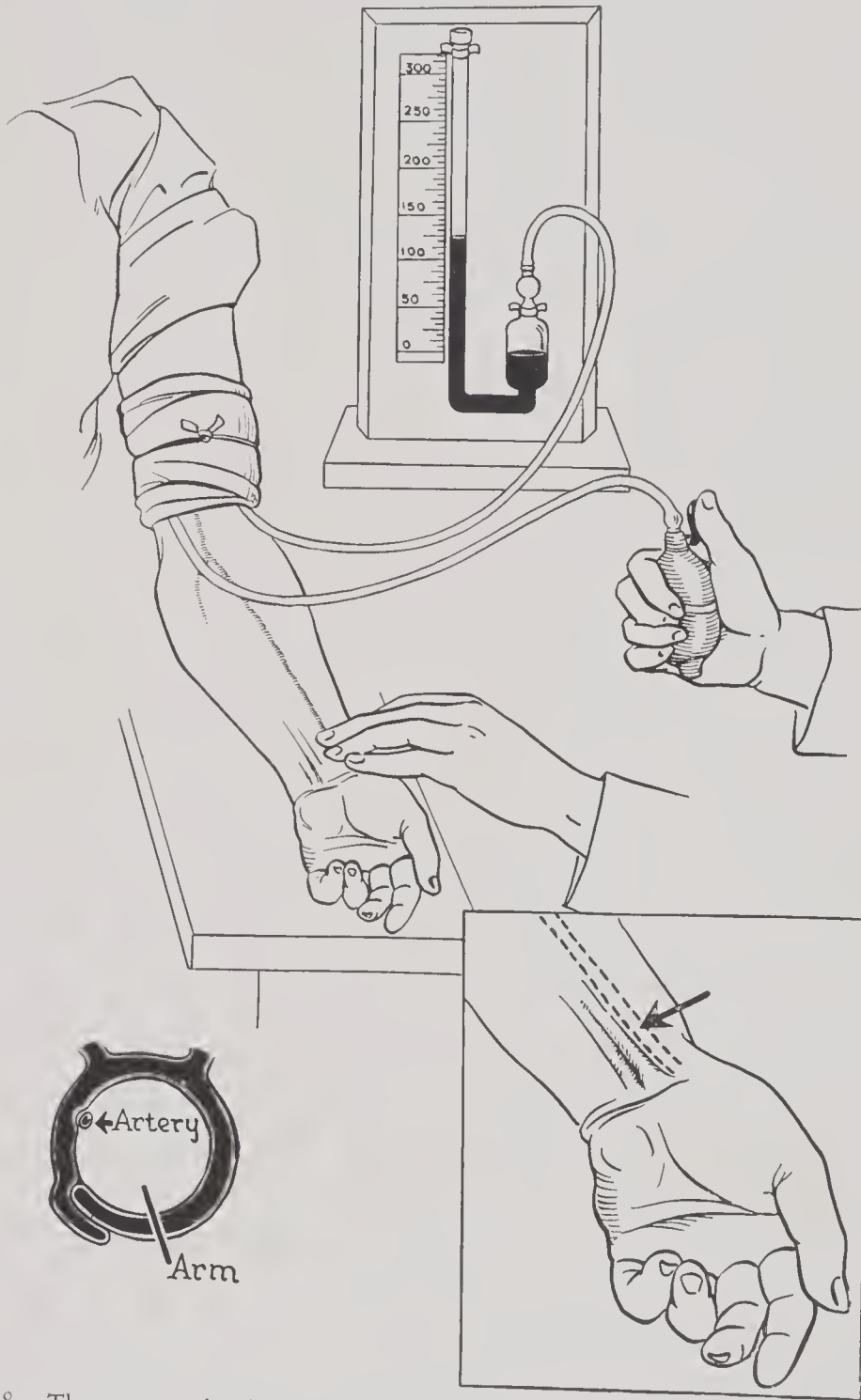


FIG. 48. The pressure in the artery is measured in terms of the air pressure which must be produced in a cuff around the arm in order to collapse the artery. This air pressure is measured by the height of a column of mercury which it will support. That the air pressure has collapsed the artery can be determined by feeling the pulse in the wrist, since this disappears when the artery is occluded. You will find the pulsing radial artery just to the thumb side of the tendons which stand out when you flex your wrist against pressure. (A still more accurate method than feeling the pulse is to listen with a stethoscope to the sounds made by the artery and blood in the hollow of the elbow.) (Drawn by E. M.)

flood into all heart chambers, relaxed during a scant half-second pause before resuming their interminable labor.

Attendant phenomena. The all-important heart beat has been intensively studied. Fine hollow needles thrust into the heart's cavities have given a continuous record of pressure changes; the pulses in arteries and veins have been measured by various methods; close-fitting cups placed over the ventricles or whole heart follow accurately the exact amount of blood entering or leaving its cavities; and, especially useful in man, the action potentials of the contracting heart muscle, recorded from arms and legs, give an electrocardiogram which yields precious information about the timing, strength, coordination, and other properties of the beating organ. But simpler indices are available to anyone with ears and fingers. The impact of the tip of the ventricles against the chest wall, about an inch below the left nipple, can be seen and felt with each beat. More information is obtained by pressing your ear or a stethoscope against the chest just to the left of the breast bone about a third of the way down. You will distinguish a double sound, the first, low-pitched and booming, the second, sharper, briefer, and rather snappy. The first sound comes largely from the contracting heart muscle, the second is caused by the snapping together of the leaves of the valves at the orifices of the arteries.

If the aortic valve, for example, has been infected and partially shriveled by the resultant scar (an all too common consequence of rheumatic fever infection in children), its leaves will not close perfectly and some blood will leak back into the ventricle during diastole. The second sound will then be blurred and continue into a distinct murmur, as of liquid forced through a small opening. A similar leak in the A-V valves causes a like murmur during the first sound, when ventricular systole squirts part of the blood into the auricle.

A heart with a moderately leaky valve can function quite well over long periods. Some of the blood which should have been forced on through the arteries at each beat backs up instead; but if the heart manages to pump more blood at each stroke some could regurgitate and an adequate amount still

go forward. This is just what happens. The leaky heart gradually enlarges, its muscular walls become thicker and stronger, that is to say it hypertrophies, and the body receives its proper blood supply. On the other hand, such a heart would hardly have the normal reserve capacity to meet emer-

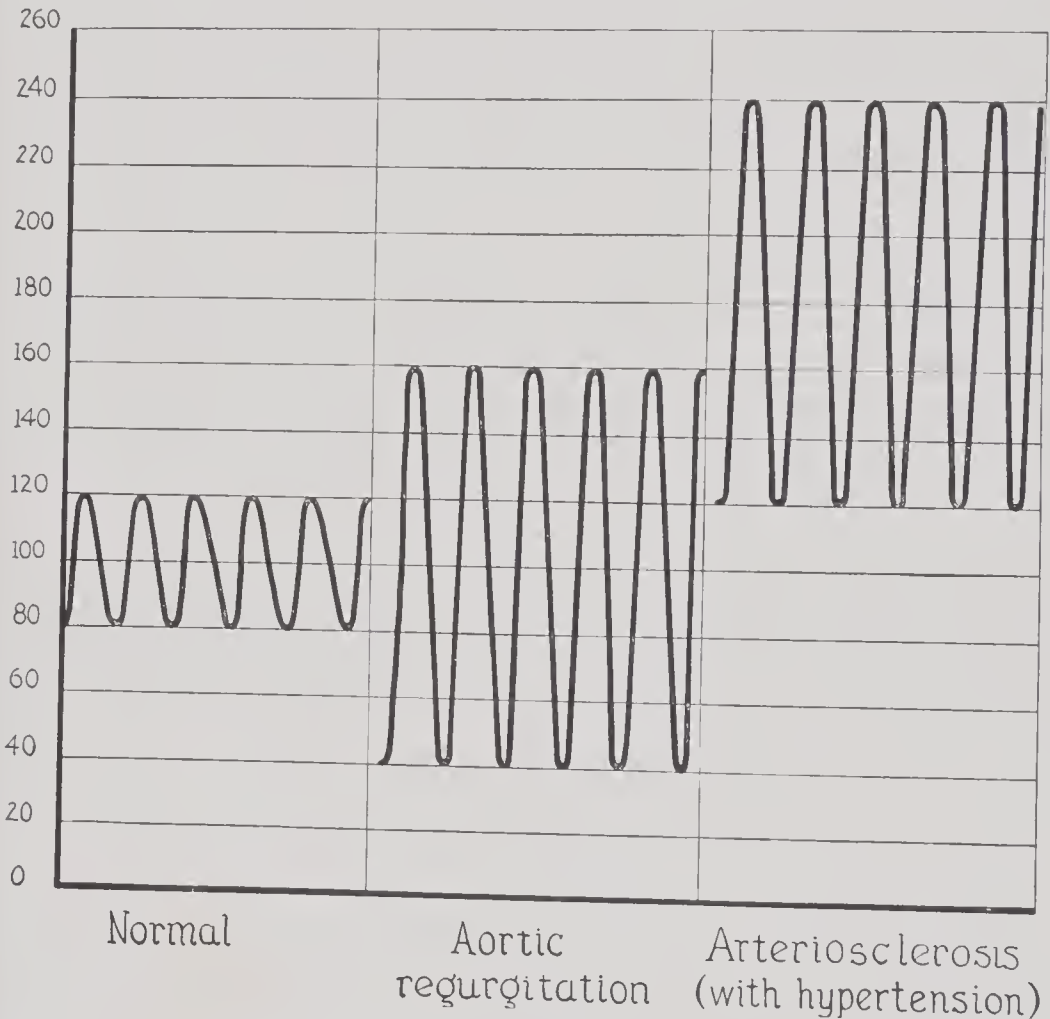


FIG. 49. This diagram shows the systolic and diastolic pressures (and the pulse pressure as the difference between them) in the normal adult, in one suffering from aortic regurgitation due to a leaky aortic valve, and in one with severe arteriosclerosis and high blood pressure. (Drawn by E. M.)

gency demands; and persons with leaky valves must avoid undue exertion.

The reasons for another effect of a leaky aortic valve you can surely figure out. The systolic pressure in the arteries is higher, and the diastolic pressure lower, than normal; i.e., the change in pressure during a pulse, pulse pressure, is much greater than it should be. This same great swing in arterial

pressure, from extra high to extra low, is also seen in cases of definite hardening of the arteries; again, explain this yourself.

Control of the beat. How is the heart beat controlled, and how are the auricles and ventricles made to contract at exactly

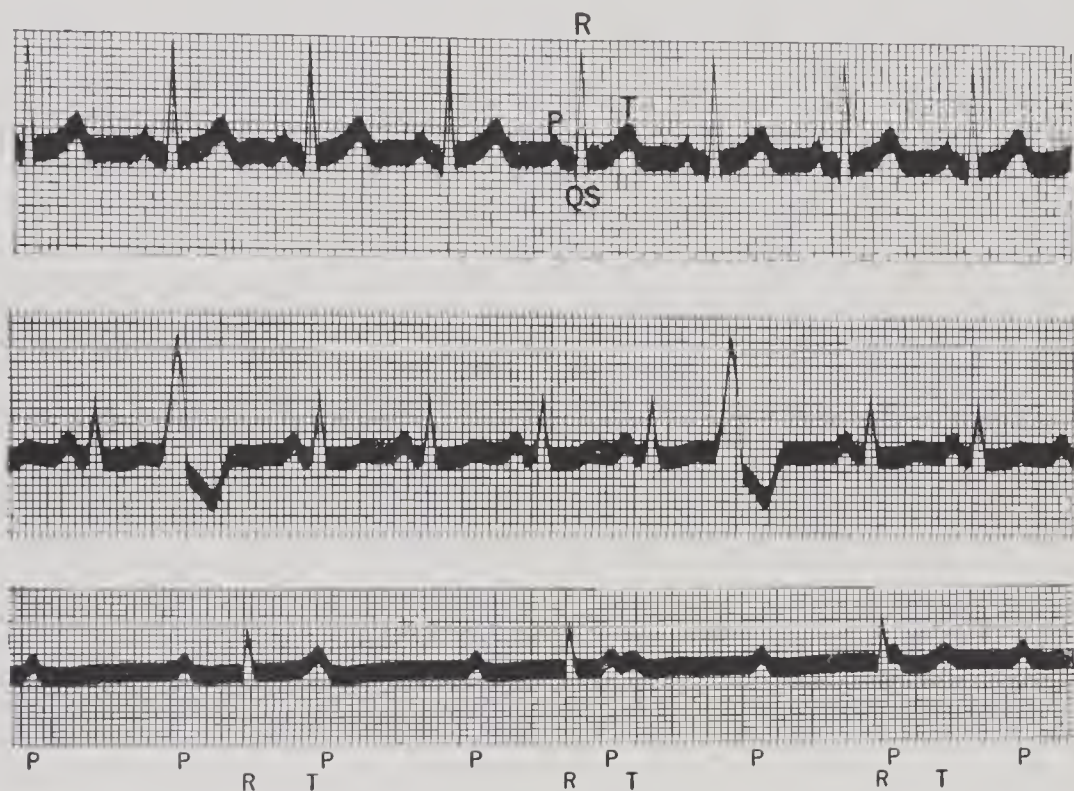


FIG. 50. These three electrocardiograph records show the normal heart beat above and two types of disturbance below. The large sharp vertical spike (*QRS*) and the smaller wave following (*T*) are produced by the ventricle. The small rounded wave (*P*), which just precedes the spike in each normal beat, is due to the auricle. In the normal record, the regularly repeated sequence of auricle beat, then ventricle beat, is clear. The second record shows two extrasystoles breaking the ventricular rhythm. Aside from the changed shape, which is unusual, note that each premature beat of the ventricle is followed by a longer interval than normal so that just one normal beat is lost from the regular rhythm. In the lowest record, the excitation to beat, which travels from auricles to ventricles, has been entirely interrupted by disease (complete heart block) so that the auricles are beating regularly at one rhythm, the ventricles more slowly at an independent but equally regular rhythm. (Courtesy of Dr. Louis N. Katz, Michael Reese Hospital.)

the right interval? We saw earlier that after a premature beat, caused by an electrical stimulus, there is an extra long pause before the next normal beat occurs. The same sort of “extrasystole” and subsequent wait occur in man when disease produces local irritation in the ventricle and thereby an occasional irregular stimulation. Presumably, then, an especially

active "center" somewhere in the normal organ sends out regular stimuli to the great mass of muscle. Such a region has been found, at the junction of the veins and the right auricle. If this tiny portion of the auricle's wall is cooled, the whole heart beats more slowly; whereas cooling elsewhere does not change its rate. The microscope shows in this position a small node or clump, the pacemaker node, of cells which are somewhat intermediate in structure between nerve and muscle. How this becomes spontaneously and rhythmically active we have considered in relation to rhythms. The control of the intrinsic heart beat—by accelerator and inhibitor nerves, which connect with the cells in the pacemaker, and by the various salts and neuro-humoral substances—depends largely on action upon this node.

But how does the beat, initiated in a far corner of one auricle, spread through the whole heart to the apex so as to produce properly timed contractions? Here is the same problem of conduction encountered in skeletal muscle and nerve, but with a complication. If the excitation spreads rapidly, the whole heart should contract practically simultaneously; if it spreads slowly, contraction should travel from end to end, rather like a peristaltic wave. Neither situation would account for the slight delay between the systoles of auricles and of ventricles, while all parts of each chamber contract practically simultaneously. The answer lies in the further distribution of these special nodal cells. From the pacemaker, many short branches of nodal tissue radiate through both auricles, excitation spreads rapidly along them, and all regions of these two chambers contract together.

No true muscular connection exists, however, between auricles and ventricles; they are held together by a fibrous ring at the level of the A-V valves. In the heart wall between the right and left rings is another node of these special cells, the A-V node, which receives thin strands of nodal tissue from the pacemaker. From the A-V node, in turn, a good-sized bundle runs down the wall between the ventricles to the apex of the heart, giving off numerous branches to the muscle along

its length. The discharge from the A-V node spreads rapidly throughout the ventricles, as did that from the pacemaker through the auricles; but there is just the right delay, after the pacemaker has discharged, before the A-V node is able to follow suit. If the A-V node, or the bundle leaving it, is cooled, the heart rate is not changed, but the delay between the start of auricular systole and that of the ventricles is increased; and if either of these nodal structures is destroyed, the auricles continue to beat normally but the ventricles stop,

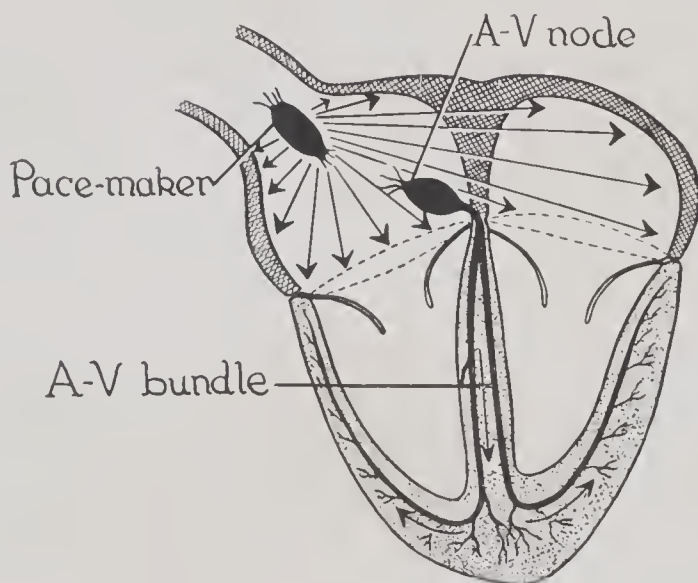


FIG. 51. The special "nodal" tissue, distributed through the heart walls, originates (at the pacemaker) and carries to the muscle (via the A-V node, A-V bundle, etc.) the stimulus to contract. (Drawn by E. M.)

or beat irregularly, or even continue to beat at an independent rhythm considerably slower than that of the auricles. (See Fig. 50.)

BLOOD FLOW. The steadily beating heart ejects into the aorta 60 to 70 cubic centimeters of blood at each stroke, seventy times a minute.*

It thus pumps 4 to 5 liters of blood a minute and, since there is only this much blood in your whole body, it follows

* How much blood must be pumped into the pulmonary artery; what would happen if the amount were greater or less than that passing through the aorta; and how can you account for the perfect balance that is obviously maintained?

that, on the average, a bit of blood must make the complete circuit from left ventricle back to left ventricle within a minute. Actually, since some blood is held in reservoirs, the circulation time averages less than half a minute. About 10 seconds are taken in the pulmonary circuit between right ventricle and left auricle, so that in 15 seconds the blood travels through, say, 2 feet of arteries, 1 millimeter of capillary, and 2 feet of vein from left ventricle back to right auricle. Most of this time is spent in the veins along which the blood seeps under low

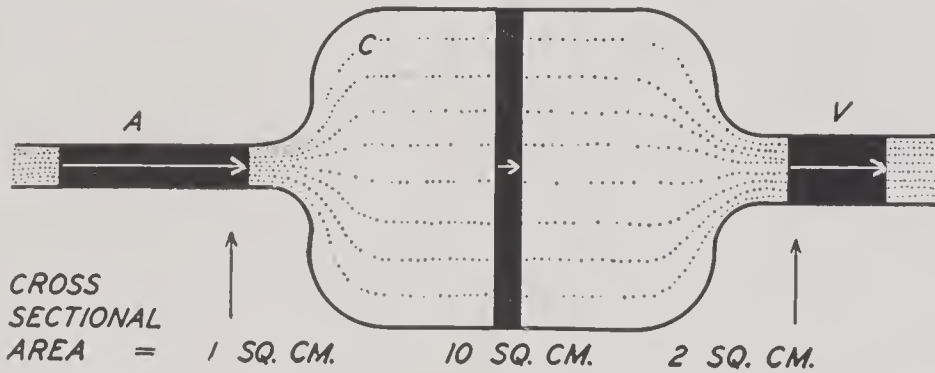


FIG. 52. This diagram illustrates the inverse relationship between cross-sectional area (indicated by the width of the channel) and velocity of blood flow (indicated by the length of the white arrow in the black bar). Since, at every instant, the same volume of blood must pass any given cross-section in the arteries (*A*), capillaries (*C*), or veins (*V*)—else it would dam up in some region—velocity times cross-sectional area must be a constant. This is shown in the diagram by the fact that the black bars have the same area in the three parts of the vascular bed. (Carlson and Johnson, *The Machinery of the Body*, University of Chicago Press, by permission of the authors and publishers.)

pressure. Yet the actual flow is slowest by far in the capillaries themselves—which is very fortunate, since only during the second or two in them can the blood perform its real functions.

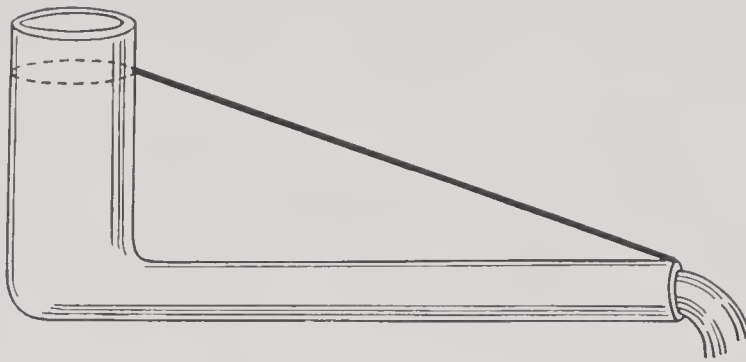
The relative rate of flow in any part of the circulatory bed depends simply on the total caliber of all alternate paths there open to it, i.e., on the cross-sectional area of the cavity. All the blood passes through the aorta and, collectively, through all its branches. Though each branch has a smaller caliber than the original artery, all together have a larger one; and since the same amount of blood must travel through each segment of the circuit, it has to move faster in the aorta than in its branches. The difference here is slight, but, as each branch

repeatedly rebranches, the total cross section increases; so that the billions of capillaries, microscopic though each one is, together offer an enormously wider passage than does the aorta. The flow in them must be correspondingly slow. As these channels again join to form ever larger but fewer veins, the cross section is again decreased and the blood flows ever more rapidly until it reaches the heart. But, the veins being of larger caliber than the arteries, the flow in them is never as rapid as on the arterial side.

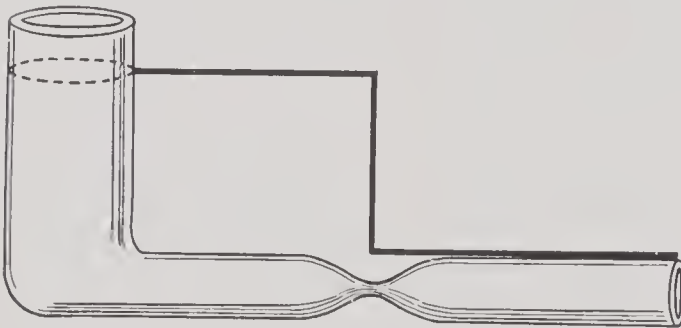
The situation is much like that of a small rapid stream emptying into a lake which is drained by a larger and slower river. While the lake maintains its level constant, as much water must run out of its lower end as enters its upper one, and this same amount must pass each cross section of the lake. A rapid current in the stream, a gentle one in the larger river, and an almost negligible flow down the great body of water are needed to produce this movement.

BLOOD PRESSURE. The story of blood pressure is quite different. Though water can easily pass from a slowly moving lake to a rapidly running river, it can certainly not move uphill from a region of low pressure to one of greater. The pressure in the vascular bed, therefore, must fall continuously from the average value of 100 millimeters of mercury in the aorta to zero in the veins near the heart. Continuously, but not linearly; for the pressure lost in passing through any portion of the conducting tubes varies with the resistance to flow offered by that portion.

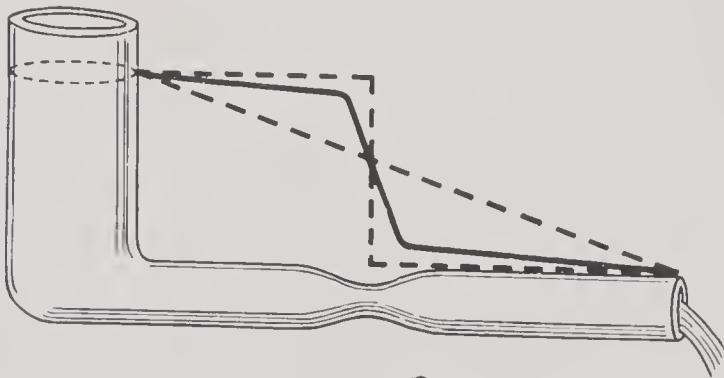
When water flows from a tank through a pipe of constant bore, the pressure exerted against the walls is greatest where it enters, falls in proportion to the distance traveled, and is least where it leaves. If, however, a valve is closed somewhere along the pipe, but the outflow end is left open, the pressure beyond the valve will promptly fall to zero while before it the pressure will rise to equal that at the reservoir end (Fig. 53). With the valve partly closed, flow will continue and the distribution of pressure in the pipe will be intermediate—it will



Open



Closed



Partly closed

FIG. 53. A diagram of the distribution of fluid pressure in a pipe discharging a reservoir when the flow is completely free (above), completely blocked (middle), and partially blocked (below). The situation in the bottom diagram is much as that in the blood vessels, with the capillaries supplying the obstruction (and the heart replacing the reservoir). (Drawn by E. M.)

fall very slowly and regularly from reservoir to valve, suffer a sharp drop at the region of the valve, and then again fall slowly and regularly to the outlet.

This is approximately the situation in the blood vessels, with the capillaries replacing the valve. Though their cross section is great, they nonetheless offer a tremendous resistance to flow. For one thing, there is enormous friction as the liquid is dragged along close to the stationary wall; and, for another, the diameter of a capillary, as little as 5 microns, may be less than the 7 microns of a single red blood cell, so that these have to be squeezed and deformed in pushing through. Further, the muscular arterioles are usually kept constricted. All in all, therefore, the great pressure fall is in the few millimeters length at the capillaries, out of the several feet of total circulation distance.

Rereading the discussion of blood-pressure regulation, in the last chapter, may now throw a new light on how this "peripheral resistance" helps to control arterial pressure and blood flow. Remind yourself also of the nervous mechanism which, by regulating peripheral resistance and cardiac output, keeps blood pressure constant; and of the chemical mechanism which, by locally controlling the caliber of arterioles and capillaries, regulates the blood flow to a particular region.

One added point on local flow. Even if all the tiny vessels in an organ, say a muscle, were wide open the amount of blood flowing through it would still be limited by their total number. We might expect that the number of capillaries per given volume, and so the potential supply of blood, would vary with the metabolic rate of an organ. This is roughly true, and is one reason why the mucous membrane of your lip, for example, composed mainly of living cells, is so much redder than the skin of your face, composed mainly of dead ones; and why a tear in it bleeds more freely. The following figures, stating the number of cubic centimeters of blood which pass in a minute through a hundred grams of the organ, give some idea of relative metabolic intensities: whole leg, 5; resting muscle, 12; intestine, 70; brain, 150; thyroid gland, over 500.

FAILURE OF THE CIRCULATION. Some final words on how circulation mechanisms break down to result in inadequate flow and low pressure. You have noted the local effects of occlusion; you are also familiar with the general circulatory breakdown of ordinary fainting. In this, loss of consciousness is caused by failure of the oxygen supply to the brain, due in turn to an inadequate circulation of blood through it. Less dramatic, but more prolonged and serious, is the condition of shock which follows severe injury, hemorrhage, or infection. In such cases blood flow through the tissues is simply inadequate and, one after another, their functions break down. The brain is especially vulnerable, partly because of its high metabolism, but also because, in the upright position, it suffers first when arterial pressure falls. It is undoubtedly to protect the brain circulation from the vicissitudes of rapid change between lying and standing positions that powerful pressure-regulating receptors have come to be located in the carotid sinus, just where the main artery to the brain dives in towards its goal.

Now what causes the failure of circulation? Obviously, if the heart falters or becomes feeble, or if much blood is lost, blood flow must suffer, but these are not the events that determine ordinary fainting or shock. The essential trouble is that blood returns to the heart too slowly and is simply not there to be pumped. But, barring hemorrhage, where does the blood get to? Three places: A widespread dilatation of capillaries so increases their volume that they can retain all the blood of the body; the same is true to a lesser extent of the thin-walled veins; and, finally, when capillaries dilate too far their stretched walls become more permeable and fail to hold back the plasma proteins (the osmotic pressure of which normally keeps the plasma water from filtering out), and the entire liquid portion of the blood seeps out—producing edema of the tissues and leaving solidly packed masses of blood cells in the capillaries.

This last condition is obviously the most serious one and can be met only by transfusing into the vessels additional fluid,

preferably blood, to restore an active circulation. But the pooling of blood in capillaries and veins can be remedied if these are made to constrict and disgorge their stored blood into the circulation. Certain vasoconstrictor drugs, as adrenalin, are often helpful here; but in ordinary fainting the body's neural mechanisms are quite able to recover and perform this duty if only the nervous system is not too long deprived of oxygen. Since it was gravity which caused this particular brain anemia in the standing position, the adequate remedy is simply to place the fainted person horizontally, or even a little head-down.*

Finally, what actually starts the vascular disturbance? People faint when standing still for a long time while hot and tired; on suddenly standing up after lying relaxed in bed, especially if warm to begin with; and under conditions of emotion—the sudden sight of blood, distressing news, and similar shocks. From your knowledge of the influence of gravity, of the vasodilation which occurs in the warm body, and of the constant delicate control of blood vessels from the nervous system—recall your sudden flushing when embarrassed—you can surely supply the additional details.

* The importance of position is easily shown in about a third of normal individuals. If one is strapped loosely to a table that can be tilted, he remains perfectly comfortable while horizontal or when tilted head-down. But when turned head-up, nearly in a standing position yet with relaxed muscles failing to produce their normal milking action on the veins, he will faint dead away in two to five minutes.

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CHAPTER VII

GAS EXCHANGE

THE RESPIRATORY SYSTEM. It is now evident how crucial to the body welfare is an adequate supply of oxygen and removal of carbon dioxide. When circulation fails it is lack of oxygen which earliest disrupts cell function, and an entire extra blood circuit through the lungs is built into your anatomy to guarantee that no bit of this fluid fails to take on its precious cargo in the course of each voyage. The functioning of the respiratory system is in principle extremely simple. Just as the chemical exchange between blood and cells can occur only through the fine thin-walled capillaries of the body, so the oxygen and carbon dioxide exchange between blood and air is consummated in the capillaries of the lungs. All the rest of the story has to do with renewing this air so that it always contains more oxygen and less carbon dioxide than does the venous blood which reaches the lung capillaries.

It might seem far simpler to have the blood simply pass through capillaries spread upon the body surface, and so automatically exposed to fresh supplies of oxygen. Indeed, animals living in water or moist conditions do just this. Look at the gills of a fish, preferably a living one, and note that they are merely a richly pleated surface packed solid with fine blood vessels. Even the frog carries on a third of its respiration through its moist skin. But this simple solution is impossible to land animals since surface capillaries would promptly dry up; and if a layer of epithelium protected them from drying it would also prevent the gas exchange. By inverting a large air space into the chest, the air in it can be kept moist and exchanged cautiously in necessary amounts so that the inevitable water loss is reduced within tolerable limits.

For a good picture of a lung, think of a great bunch of grapes, shrunk to about a twentieth of its size and with the



FIG. 54. The alveoli and bronchioles of the lung closely resemble bunches of microscopic grapes and their stems. (Drawn by P. McC.)

insides removed, leaving the grape skins and the “bark” of their supporting stalks and stems. The main stem is the windpipe (trachea), running from the voice box (larynx) down into the chest. This divides into the large right and left branches, bronchi, and these into ever finer twigs, until a single bronchiole ends in its own group of air sacs or alveoli. The wall of each sac is composed of a rich network of capillaries with a minimal amount of other cells to support them.

Around each lung is the familiar slippery layer of endothelium which, like the pericardium, folds back on itself at the main bronchus to continue as a similar lining of the chest wall.

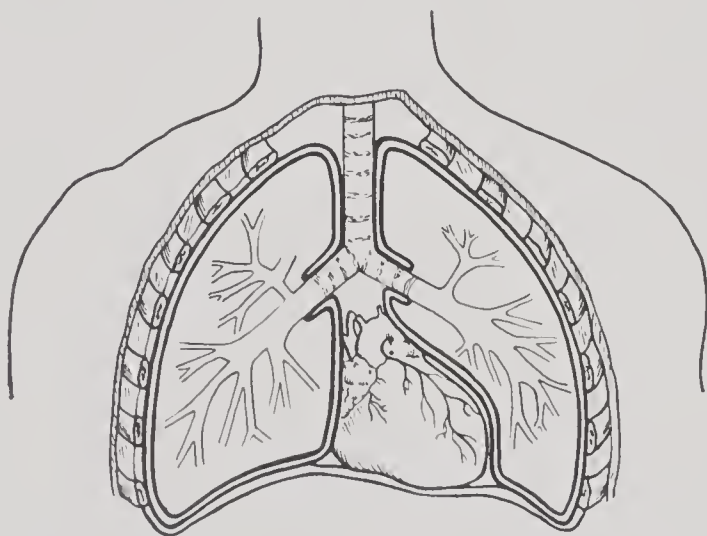


FIG. 55. The lungs, each enclosed in a double-walled pleural sac, are actually attached to the body only by their main bronchi. (Drawn by P. McC.)

Each lung, therefore, is attached to the body only by its bronchus, the remainder being entirely separated from the muscle and ribs outside it by this closed double-walled pleural

sac (Fig. 55). Most of the chest is occupied by the lungs and is divided into independent right and left cavities by a tissue wall down the middle, in which run the gullet, many nerves and blood vessels, etc., and from which the heart bulges to the left. The ribs and the "intercostal" muscles, which lie between and move them, constitute the outer walls of these roughly conical cavities; and the bottoms are closed by a great

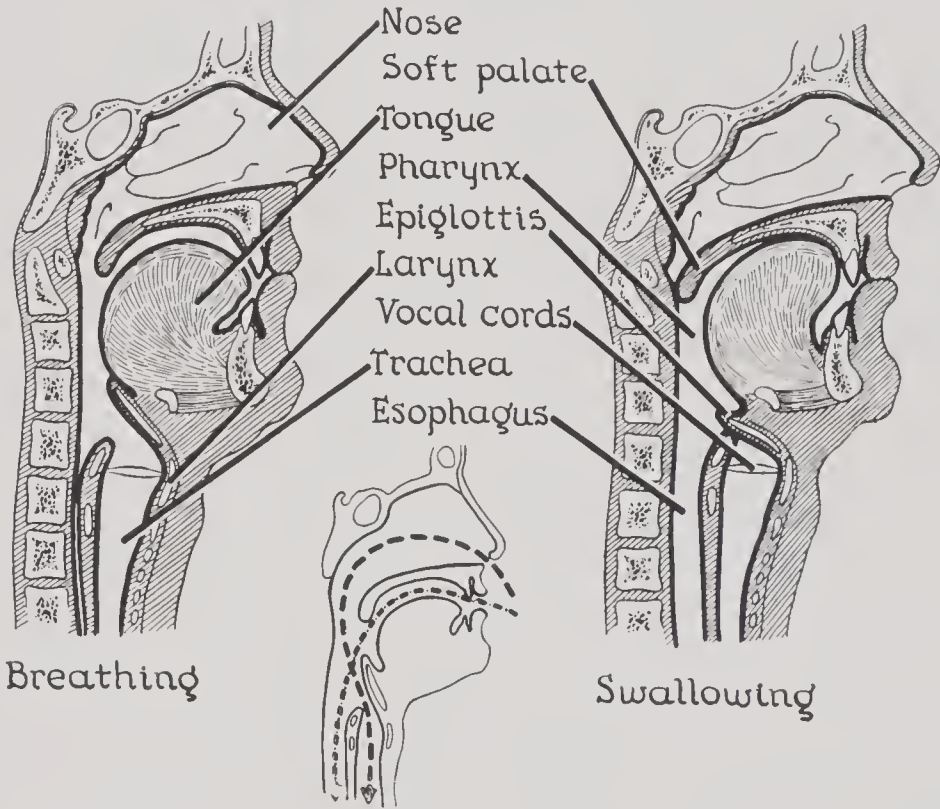


FIG. 56. During ordinary breathing the soft palate hangs down, the larynx compresses the esophagus, and the epiglottis is up, thus giving a free passage from nose to trachea. During swallowing the raised soft palate closes off the nasal passage and the larynx is pulled up and forward, which brings down the epiglottis to close it and at the same time opens the esophagus. (Drawn by E. M.)

dome-shaped sheet of muscle, the diaphragm, attached around its circumference to the lower margin of the ribs.

Safety devices. The tortuous passages through the moist and sticky mucous membranes of the nose obviously help to moisten, warm, and "filter" the outside air on its way into the lungs; and the larynx and the epiglottis, which folds down over it during swallowing, help to prevent food, saliva, and other materials from accidentally falling into the trachea

when they should have been swallowed. The use of the larynx to produce sounds for communication is a secondary and later function. Anatomically, the crossing of the respiratory and digestive passages, at their upper ends, seems to be peculiarly inept. Food must travel from mouth through pharynx to esophagus; while air must move from nose, above the mouth, through pharynx to larynx, below the esophagus. The shoddy arrangement could hardly result from a good plan, but becomes understandable in the light of evolutionary history.

The lungs appeared first, as a pocket on the front of the digestive tube; and only much later was a palate built across the oral opening, and the upper part combined with the sense organs of smell (originally little blind pits on the body surface) to make an independent air passage, and finally a true nose. Vertebrates have evolved all sorts of secondary mechanisms to mitigate the difficulties of this bad arrangement. If you were able to swallow and breathe simultaneously, for example, some food would surely enter the lungs; but this is normally impossible because of a reflex, set up as soon as food touches special receptors in the back of the pharynx, which automatically causes all the following effects: Respiration is stopped dead, by an inhibition of the respiratory center; the soft palate at the back of the mouth is raised to close off the nose (when this is paralyzed, and occasionally even in the normal, much of the food "swallowed" squirts unpleasantly from the nostrils); the larynx is pulled forward and up, automatically pulling the epiglottis down over its opening like a hinged cover on a box—you have watched the bobbing of Adam's apples while people eat; and, finally, a powerful peristaltic contraction runs down the esophagus from pharynx to stomach.

Still other safety mechanisms are held in reserve, for such a complex response as swallowing might break down—witness the occasional drop of saliva which trickles into the larynx without having stimulated the proper swallowing responses. The reaction to such an object in the trachea is, of course, an explosive cough. Receptors in the mucous membrane lining of the trachea and bronchi are stimulated by contact to send

impulses up afferent fibers of the vagus nerve; and these messages not only inhibit any inspiration but evoke as well a forceful expiration. A sneeze is a closely related response to irritation of the nasal mucous membrane though, in this case, a deep inspiration ordinarily precedes the sudden expiration. A second, continuously acting, protective device is the beating cilia of the outer epithelial cells of the mucous membrane of nose and respiratory tubes. Tiny particles settling from the air onto this membrane are slowly whipped up to the pharynx from bronchi and trachea and down to it from the nose and are eventually swallowed or expectorated, well tangled in mucus.

There is no muscle in the lungs, except for some smooth muscle fibers which encircle the individual small bronchi and bronchioles. When these contract they constrict the air passages, exactly as the similarly disposed muscles on arterioles constrict them. These muscles, therefore, help determine the ease with which air can pass to and from the lungs but can in no way bring about actual respiration.*

BREATHING MECHANICS. The lungs, then, can certainly not move themselves, yet move they must in breathing. During inspiration their cavities are enlarged, by half a liter during an ordinary breath, and during expiration are again diminished. The lungs expand because the chest cavity enclosing them enlarges. From the respiratory center in the medulla, nerve impulses are broadcast down the spinal cord and out through the dozen intercostal nerves leaving each side of it, to make the intercostal muscles contract and lift the ribs. Since these curved bones are hinged at the ends,

* When the bronchioles are too constricted there results real difficulty in breathing, especially in expiration, which you know as asthma. As usual, ortho- and parasympathetic nerves act oppositely on these muscles; you can figure out which causes contraction and which relaxation when you recall that adrenalin and atropine are both used to treat an acute asthmatic attack. Does your conclusion fit in with the statement made above that the bronchial tree is derived from the digestive tract?

like a bucket handle, they move out as they move up and so increase the width of the chest. Further, the front hinge, at the breast bone, is itself movable and actually the whole chest front goes up and forward, so increasing also the front to back dimension. Perhaps most important, one phrenic nerve leaves each side of the spinal cord low in the neck, runs down each side

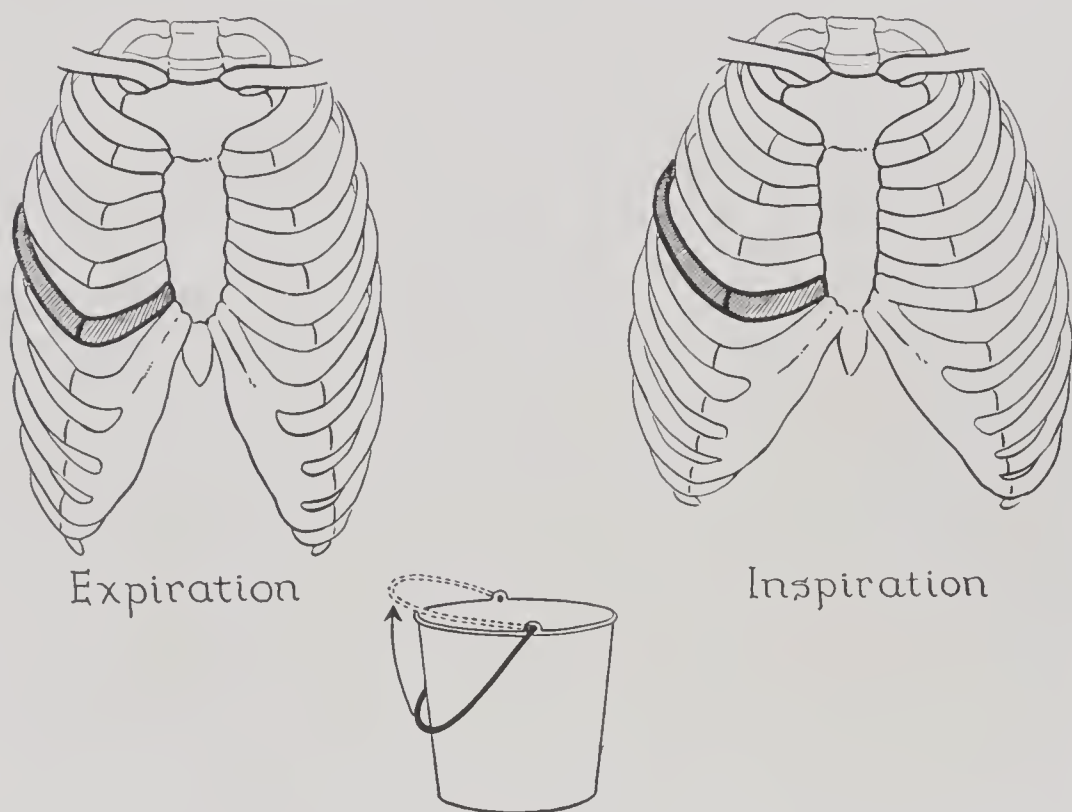


FIG. 57. Each rib, attached to the spinal column behind and the breastbone in front, rather like the handle of a bucket, moves outward as it is pulled up. In addition, since the whole breastbone also moves up slightly and the ribs slant down to it, the distance from vertebral column to breastbone is also increased. Finally, the downward movement of the diaphragm increases the third, vertical, dimension of the chest as well as the other two. (Drawn by E. M.)

of the middle wall of the chest to the diaphragm, and, carrying some of the impulses which originated in the respiratory center, makes this muscle contract. (There is good evidence from the comparative study of vertebrates that the diaphragm has evolved from a muscle in the neck which gradually migrated tailwards. This accounts for the peculiar origin of its motor nerve, from the distant neck region of the spinal cord rather than from one more conveniently in its neighborhood.)

Inspiration thus depends entirely on the contractions of these muscles; and expiration results when they again relax and is, therefore, purely passive. True, as the diaphragm pulls down its dome, the abdominal viscera must make space for it; and this is achieved by a relaxation of the muscles of the abdominal wall—note on yourself that the belly wall bulges out when you inspire. Conversely, a powerful contraction of the abdominal muscles can force up the diaphragm and pull down

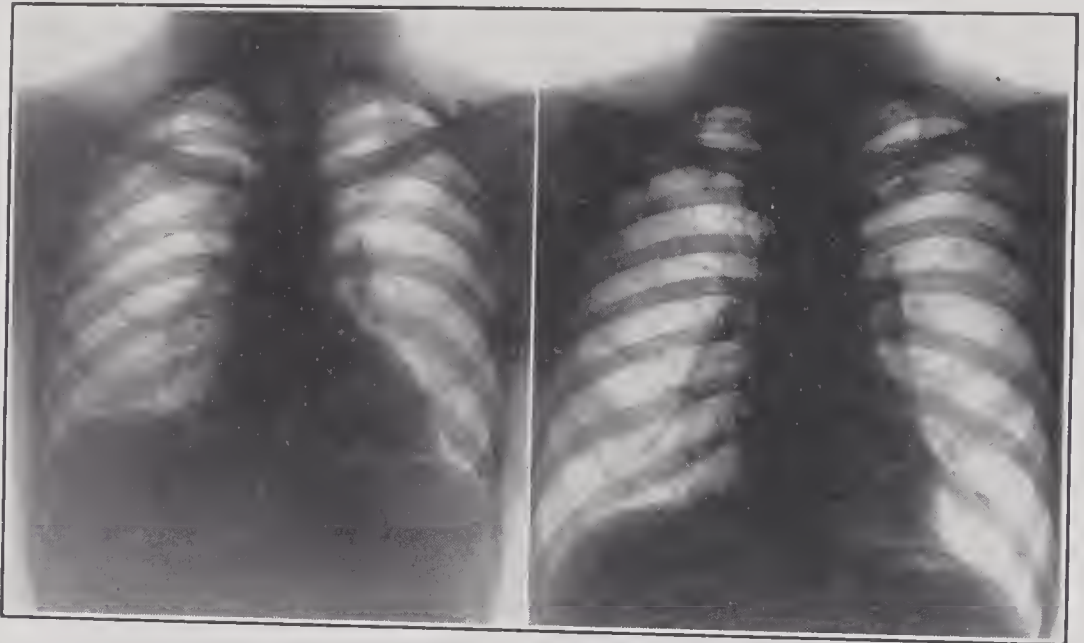


FIG. 58. X-ray photographs of a normal chest taken at the end of expiration (left) and at the end of inspiration (right). Note the raised ribs, lowered diaphragm, greater air space, and more pendant heart after breathing in. (The lungs themselves do not show except as occasional calcified lymph glands and bits of bronchi throw a lacy shadow in the otherwise clear air space.) (Courtesy Roentgenology Staff, Billings Hospital.)

the ribs to give a forceful, active expiration. This mechanism does not occur in quiet breathing, but when you cough, or blow against resistance, feel how your abdominal muscles contract to aid in squeezing out the air. During straining at stool the larynx is kept closed after a deep inspiration and then the abdominal muscles contract. The trapped air and the low tense diaphragm help direct the increased abdominal pressure against the contents of the rectum rather than allow it to empty the chest.

The chest walls move out, then, because the muscles in them contract; but why should the lungs follow? The double-walled pleural sac, you remember, leaves the lungs attached only at the central chest partition; further, elastic fibers in the lungs, like those in the arteries, are kept continuously stretched and so attempt to collapse the lung. This

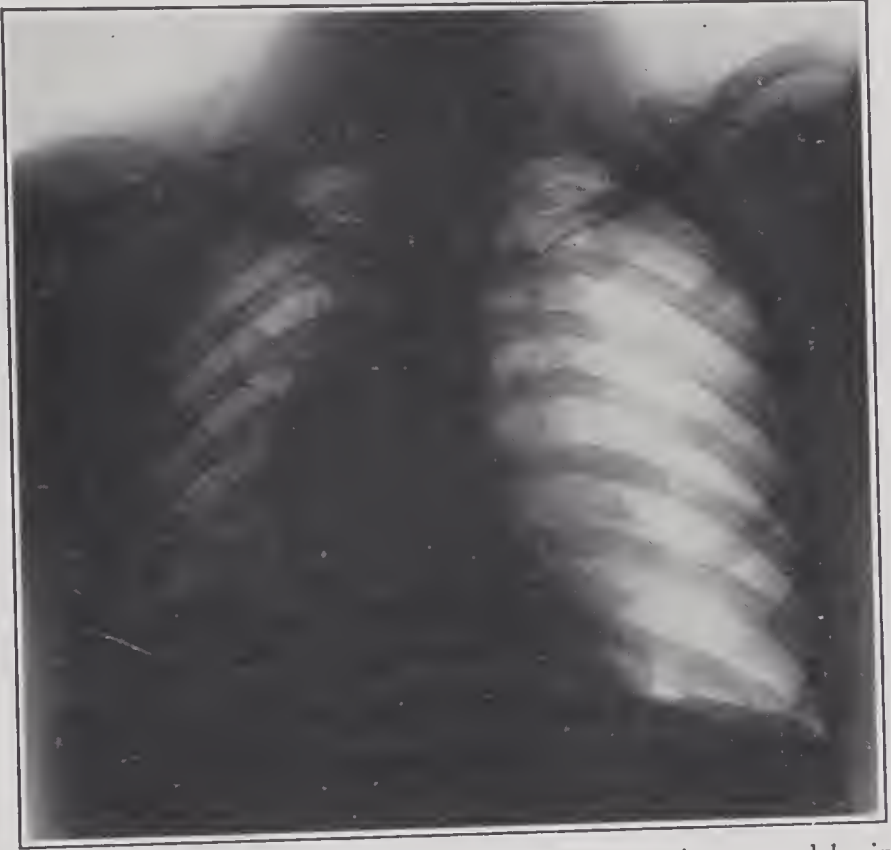


FIG. 59. X-ray photograph of the chest of a tuberculous patient treated by introducing air into the right (as seen) pleural cavity (artificial pneumothorax). Note the outline of the collapsed lung on the right side near the middle of the air space. The diaphragm is markedly depressed and the chest wall bulged on the treated side. (Courtesy Roentgenology Staff, Billings Hospital.)

is simply demonstrated when the chest wall is punctured; the lung promptly shrivels and forces its contained air out through the bronchus, like a toy balloon when its nozzle is untied. Outside air rushes in through the hole in the chest to occupy the enlarging cavity between the chest wall and lung, within the two layers of the now opened pleural sac. Such a "pneumothorax" is sometimes produced deliberately on one side to treat tuberculosis. Sterile air is admitted to the pleural

cavity through a hypodermic needle and the injured lung thus allowed to collapse and remain at rest while the chest wall continues its regular breathing movements.

Pressure in chest and lungs. What, then, keeps the lung from collapsing even when the chest is closed, and what makes it follow so obediently when the chest enlarges in an inspiration? Think again of the toy balloon. This can be distended not only by blowing air into it, to make the inside air pressure greater than the atmospheric pressure outside, but also by sucking away the air surrounding it (with the balloon in a closed bottle) while leaving the nozzle of the balloon, and so the contents, open to air at atmospheric pressure (Fig. 6o). The balloon will expand until the pull of its stretched elastic wall is great enough just to balance this pressure difference, as a rubber band stretches under a weight until its elastic pull is equal to the pull of the weight.

The spaces within the lungs themselves are always freely open to the atmosphere, and the air within them is, therefore, at atmospheric pressure when the lungs are still. (At the beginning of inspiration, the pressure in the expanding lungs is very slightly below atmospheric, which is why the air rushes in; but by the end of inspiration the pressures are again equal. Similarly at the start of expiration, the pressure rises slightly and so causes air to flow out.) The pleural space outside the lungs normally contains no air, and only a negligible amount of fluid, but this is under a suction or traction or "negative pressure" due to the elastic pull of the lungs; and if these organs failed to follow snugly against the chest wall a true vacuum would be produced. A far stronger wall than the delicate lung surface would be needed to hold it.*

Are you wondering how the lungs ever managed to get stretched in the first place? The fetus lies in the womb curled

* Though the lungs follow the chest wall, they slide against it in the lower portion to fill the angle left when the diaphragm moves down. The slippery pleura makes this easy, but when this membrane is inflamed and roughened in pleurisy, each breath causes a sharp pain, and a rough scratching sound in the doctor's stethoscope.

up like a sleeping kitten, with head and knees pressing upon its collapsed and air-less chest. As it is born it straightens and soon gives its first sucking cry. The chest cavity greatly enlarges, the lungs are sucked out with it, and the first air rushes

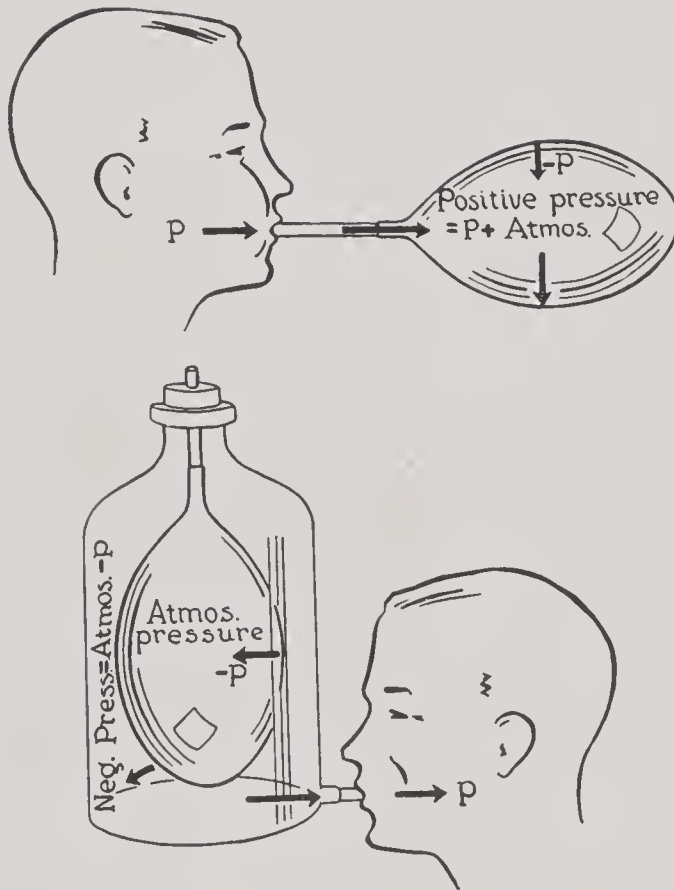


FIG. 60. As a rubber balloon is stretched the elastic pressure of its wall increases. The balloon will always reach such a size that this inwardly directed pressure ($-P$) is just equal to the difference in gas pressures inside and outside of it. It makes no difference whether the inside pressure is increased above atmospheric by blowing into the balloon, or the outside pressure is decreased below atmospheric by sucking air from the balloon's container. The second case corresponds to the lungs and chest. The pressure within the lungs (intrapulmonic pressure) is atmospheric, since this cavity is open to the outside air through the bronchi; the lungs exert an elastic pull; the pressure in the pleural cavity surrounding the lungs (intrathoracic pressure) is consequently lower than atmospheric pressure by the amount of this elastic pull.
(Drawn by E. M.)

in through trachea and bronchi. This first gasp is far greater than normal respiration, so the lungs are never again emptied of air.

Chest capacity. Greater chest capacity develops with growth until, in the normal adult, even at the end of an ordinary

expiration there still remain in the lungs two to three liters of air. Something over half of this can be expelled by the most powerful expiration one can make; the remainder stays no matter how you squeeze. Just as you can force from the lungs three or four times as much air as you normally breath out, so, after a normal inspiration, you can still force in a further two to three half liters. The half liter of air which flows in and out in quiet breathing, the tidal air, is therefore hardly one-eighth of the vital capacity, the exchange between maximal inspiration and maximal expiration. There is thus plenty of reserve capacity, aside from any augmented rate of breathing, for the greatly increased gas exchange which must accompany vigorous exercise.

Ordinary breathing is a wave of inspiration and expiration regularly repeated about fifteen times a minute with little pause between cycles. Individuals differ rather characteristically in the relative durations of the separate phases; it might interest you to determine your own respiration curve. (Fig. 61.)

CONTROL OF RESPIRATION. The crux of the whole breathing process is the rhythmically repeated discharge of the neurones of the respiratory center, leading to inspiration, and their equally regular cessation of activity, which allows passive expiration. Yet, even more than is the automatic heart beat, the respiratory center is subject to a variety of external controls.

Neural regulation. For one thing, you can deliberately increase or stop your breathing (but not your heart beat) for a considerable period, showing that nerve pathways from the cerebrum reach and act upon this center in the medulla. (Voluntary control of respiration is eventually overcome in all cases by the chemical control. It is thus impossible, for example, to hold one's breath until death results, for the accumulation of carbon dioxide soon starts respiration despite the inhibition from the brain.) Other special afferent nerves likewise play upon the respiratory center to modulate its activity. We have seen how sensory fibers in the vagus, stimulated by mechanical contact on the respiratory mucosa, can

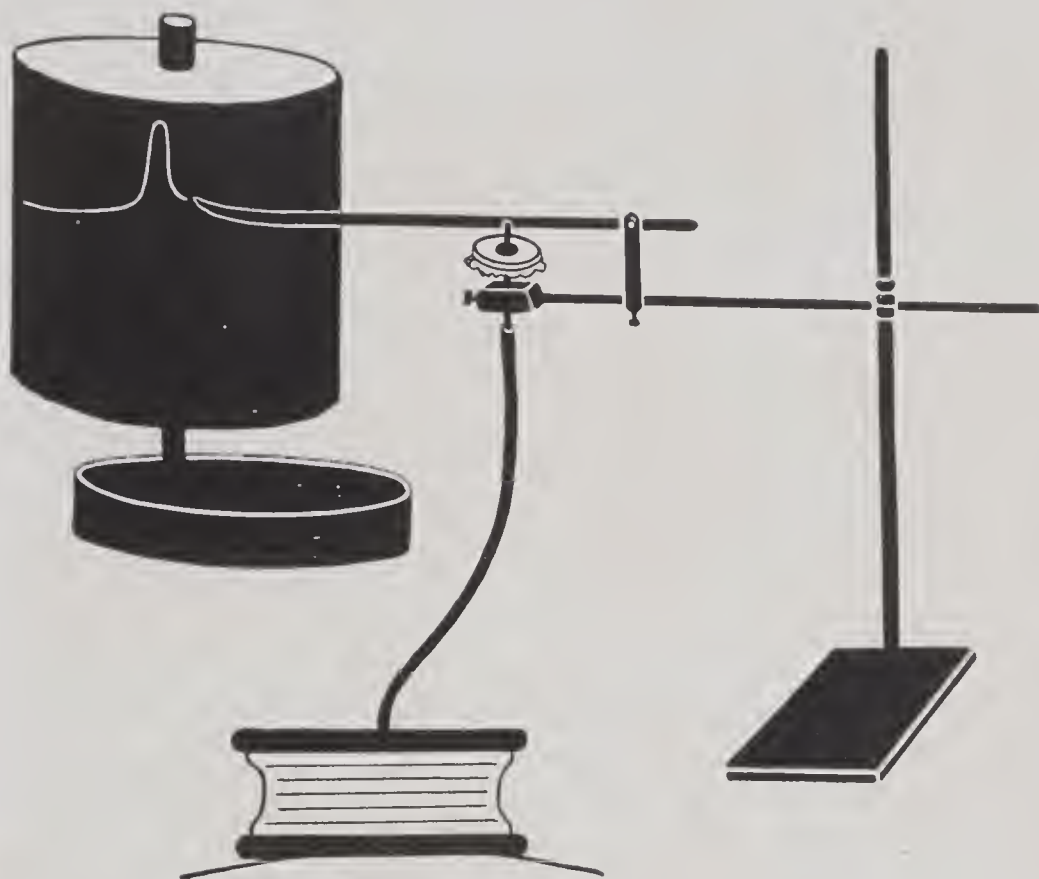
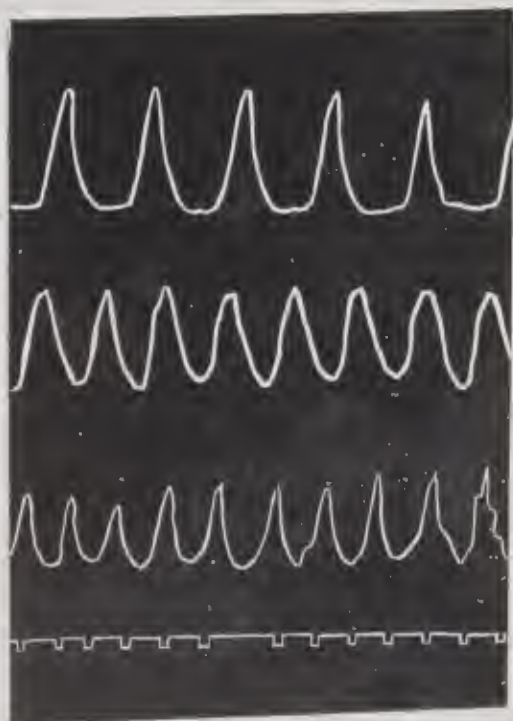


FIG. 61. Diagram of a "pneumograph" (below, resting on a chest) connected by rubber tubing to a tambour. The lever of the tambour writes on a kymograph. (Drawn by P. McC.)



Records of the breathing movements (pneumograms) of three normal individuals. Note the consistent differences in shape of and interval between the respiratory movements, from one person to another. The time marker below indicates 5-second intervals.

abruptly inhibit inspiration. Similar vagal afferents from the lungs themselves perform a like service under conditions of ordinary breathing.

As inspiration gets under way, the receptor endings in the pleura are progressively stretched. Nerve impulses carried from them up the vagus become more and more frequent as the stretch increases—as in the case of other receptors. These impulses act to inhibit the respiratory centers and, in sufficient number, cut short the inspiratory discharge. Another less important group of receptors and afferents, also in the vagus nerve, seems to have the opposite action; collapse of the lung sets up impulses which help stimulate the respiratory center to initiate a new inspiration. Here, then, is another automatic control, tending to prevent excessive inspiration or expiration. (See Fig. 62.) These nerves are, however, only secondary regulators—remember that respiration continues with all afferent nerves to the centers destroyed.

Other afferent nerves, from almost any part of the body but especially those which serve pain sensation, act upon the medullary centers to increase the depth or frequency of breathing (hyperpnea); and a special group from the skin, connected to cold receptors, causes a deep inspiration which is held—the gasp and stopped breathing (apnea) which follow your plunge into cold water. But perhaps most important are afferents from a special portion of the carotid sinuses. We have seen how pressure receptors in these small bodies help control blood pressure; their chemical receptors similarly aid the regulation of breathing.

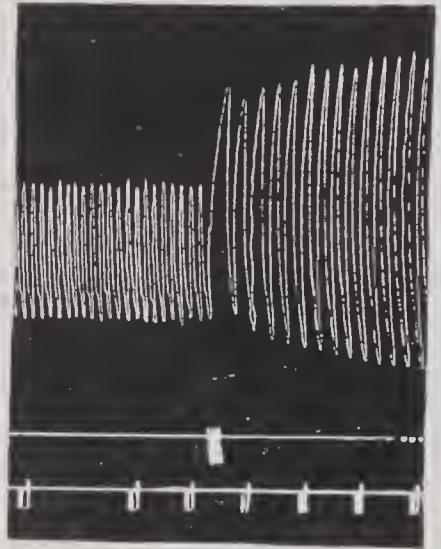


FIG. 62. Record of the respirations of an anesthetized dog before and after cutting both vagus nerves. Read from left to right; the moment of cutting is shown by the mark on the upper horizontal line. The lower line indicates time in 5-second intervals. (Carlson and Johnson, *The Machinery of the Body*, University of Chicago Press, by permission of the authors and publishers.)

Chemical regulation. When the carbon dioxide in arterial blood increases, it acts not only directly upon the nerve cells in the medulla, but also indirectly via the carotid chemoreceptors. They are stimulated to discharge impulses which greatly augment respiration. Similarly, a decrease of oxygen in the blood, or any interference with the use of oxygen by the cells, as by potassium cyanide, acts on the respiratory center and especially on the carotid receptors likewise to increase respiration. A decrease of blood carbon dioxide or, less effectively, an increase of oxygen, correspondingly leads to diminished or stopped breathing.

It is worth noting some striking similarities and differences in carotid sinus activity and that of the adrenal gland and autonomic nervous system. In the latter case, the action of nerve impulses on effectors is reinforced by the liberation of adrenalin under the influence of some of these nerve impulses. In the former, the action of a chemical on nerve cells is reinforced with nerve impulses set up by the action of this same chemical on special receptors. What, now, of the chemical changes of respiration which, after all, give significance to the mechanical and the neural processes?

GAS EXCHANGE IN THE LUNGS. The air we inhale contains, the world over, 20 per cent of oxygen and a negligible amount of carbon dioxide; that we breathe out contains about 16 per cent of oxygen and 4 of carbon dioxide. These latter values, however, must be corrected, for almost a third of the tidal air inspired never passes the bronchial tree on its way in, and is blown out again unchanged. To obtain the true composition of the air in the alveoli, the air forced out after a normal expiration must be collected and analyzed.* Careful experiments have shown the composition of alveolar air to be surprisingly constant from moment to moment, and

* You can easily prove that considerable carbon dioxide is given off in your breath, by exhaling a few times through a tube dipped in lime water—a white precipitate of calcium carbonate soon forms; but it is a little more troublesome to measure the exact amount.

even from person to person; it contains 14.2 per cent of oxygen and 5.5 per cent of carbon dioxide. Note that each breath changes these concentrations but little; for the 350 cubic centimeters of fresh air which enter the alveoli constitute hardly one-eighth of the gas already in them.

This constancy results from the balance between the continued action of the blood in the pulmonary capillaries, which takes out oxygen and puts in carbon dioxide, and the exchange of alveolar air with fresh air. Since the blood gas exchange depends on activity of other body parts, and is therefore not under control of the respiratory system, it must be the air exchange which is regulated to keep in step. Breathing is controlled by the carbon dioxide in arterial blood, right enough, but this in turn depends on its concentration in the alveolar air to which this blood was exposed in the lungs. Carbon dioxide and oxygen diffuse between blood and alveolar air and, though only the second or two in the capillaries permit exchange, the gas concentration in the arterial blood leaving the lung is nearly that which long contact would have produced.

If, therefore, the air exchange, at a certain rate and depth of breathing, were not blowing carbon dioxide out of the alveoli as fast as this gas diffused into them from the venous blood, the alveolar carbon dioxide would increase in concentration; that in arterial blood would follow, the carotid sinuses and respiratory centers would be stimulated, breathing would increase, and the alveolar carbon dioxide would be lowered to its proper level. The accuracy of this control is shown by the fact that an increase in alveolar carbon dioxide from 5.5 to 5.7 per cent suffices to double respiration; and a fall to 5.3 per cent stops breathing temporarily (apnea). You can now reason out how respiration will be affected in extensive pneumonia, with blood plasma exuded from dilated capillaries to fill alveoli until perhaps half the air space of the lungs is unavailable for gas exchange. Wouldn't breathing pure oxygen instead of air be helpful?

You now have available information as to the normal rate of breathing, the amount of air exchanged at each breath,

and the oxygen removed and carbon dioxide added. You can, therefore, calculate how many cubic centimeters of oxygen are taken up, and of carbon dioxide are given off, by the body in a minute. You also know how much blood passes through the lungs in a minute, and can therefore calculate in addition just how much more oxygen, and how much less carbon dioxide, are present per cubic centimeter of arterial blood than of venous blood. The actually measured values in cubic centimeters (obtained by drawing blood from appropriate vessels, extracting their gases, and measuring each kind of gas obtained) are: venous oxygen, 0.13; carbon dioxide, 0.59; arterial oxygen, 0.19; carbon dioxide, 0.52. Be sure you do the suggested calculations to understand the real significance of these figures.

THE BLOOD AND GAS TRANSPORT. We seem now to face a serious contradiction, for the amount of oxygen that will dissolve in one cubic centimeter of water from pure oxygen is just over 0.02 cubic centimeter; and from a gas mixture containing 16 per cent of oxygen only one-sixth this much can be taken up. Yet we have just seen that one cubic centimeter of blood can take up from air 0.2 cubic centimeter of oxygen, some fifty times as much as can an equal volume of water. Similar, though less striking, discrepancies exist in the case of carbon dioxide, and there is the further difficulty with this gas that solutions of it are strongly acid relative to blood. Unfortunately the blood mechanisms, centering around hemoglobin, for carrying carbon dioxide are too complex to consider here; but we can get some idea of how the extra oxygen is handled. Clearly it is not simply dissolved in blood as in water; the greater part must be held in chemical combination. It is simple to show that this combination is with hemoglobin, for when the pigment-carrying red cells are removed by rapid centrifuging, the clear liquid plasma remaining is found to carry only as much oxygen as an equivalent amount of water.

Hemoglobin and oxygen. Over 90 per cent of the solids of the red cell is simply hemoglobin—indeed, such cells are hardly

more than sacs of this precious substance. Hemoglobin directly combines with oxygen to form a new compound, oxyhemoglobin. Hemoglobin itself is a deep purplish red whereas oxyhemoglobin is a bright crimson, so that it is easy to tell visually in which form the pigment is, nor is it difficult, with a spectroscope, to obtain quantitative data on the changes which occur. Incidentally, as you know, it is the oxyhemoglobin which gives the bright red color to arterial blood.

Many substances combine with oxygen to become oxidized, but very few can reverse this process without the introduction of powerful reducing agents. Hemoglobin and oxygen gas combine so loosely, however, that oxyhemoglobin will spontaneously break down again to its original constituents if the oxygen is allowed to escape. This means that the fraction of hemoglobin molecules which are combined with oxygen will depend on the existing concentration of free oxygen molecules. When a solution of hemoglobin is exposed to pure oxygen gas or even to air, with only 21 per cent oxygen, practically all the hemoglobin is converted into oxyhemoglobin. When this oxyhemoglobin solution is now exposed to pure nitrogen or is placed in a vacuum, all its oxygen is dissociated and lost, leaving again the hemoglobin. At intermediate concentrations of oxygen intermediate amounts of oxyhemoglobin are formed, although not in direct proportion to the oxygen pressure.

You will note in Fig. 63 that, as the oxygen to which the hemoglobin is exposed falls from the 21 per cent of air to only two-thirds this amount, there is no proportional breakdown of oxyhemoglobin. If, instead of reducing the proportion of oxygen in the gas, air itself is used under low pressure, as on ascending to considerable elevations, exactly the same effect occurs. So long as the air pressure has not fallen below two-thirds normal—about that at Pikes Peak—the blood still picks up in the lungs nearly its full quota of oxygen and carries it to the body cells.

But note, too, that when the gaseous oxygen or the air pressure falls further below normal the amount of oxygen which hemoglobin is able to take up decreases abruptly. This

is an important cause of mountain sickness and other disturbances when man ascends to altitudes much over 14,000 feet (Pikes Peak) and why, without special oxygen supply, he is unable to get along in stratosphere airplanes. However much fresh air he breathes, the oxygen in his alveoli is at too low a pressure to combine with much hemoglobin and be carried to the tissues. Normally, however, with the alveolar

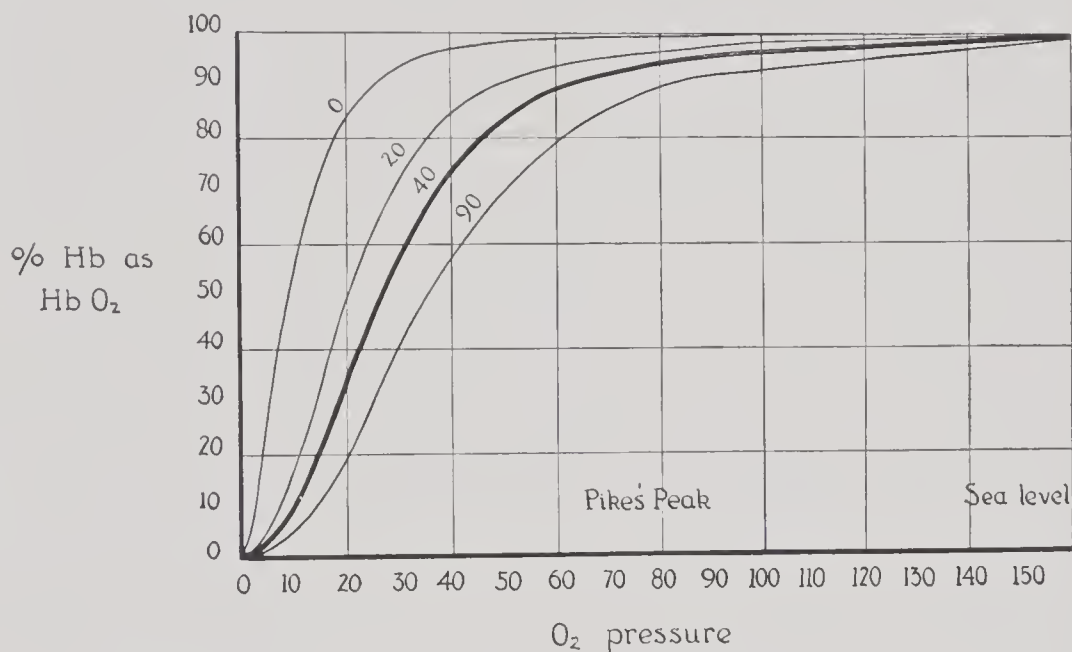


FIG. 63. The "oxygen dissociation curve" of hemoglobin is shown at four different carbon dioxide pressures, indicated above each curve. It is necessary to consider the carbon dioxide present, since it has a marked influence on the amount of oxygen with which hemoglobin will combine at any particular oxygen pressure. This action of carbon dioxide is, in fact, very important in the normal functioning of hemoglobin as a carrier of both gases, although we are not able to discuss this relationship. The normal carbon dioxide pressure in arterial blood is a little over 40 millimeters, so that the heavy curve shows approximately the condition in blood. (Drawn by E. M.)

air containing 16 per cent of oxygen, the hemoglobin molecules in the red cells sweeping through the lung capillaries are rapidly changed to oxyhemoglobin. On reaching the tissues, the blood must now approach equilibrium with body fluids containing far less oxygen, since the cells are continually using it up, and much of the oxyhemoglobin consequently unloads its oxygen.

The tremendous importance of hemoglobin in transporting oxygen is shown by the disastrous consequences of blocking this

function. Hemoglobin can combine with carbon monoxide even more readily than with oxygen, to form the bright cherry-red carbon-monoxymoglobin. This compound can also dissociate when all carbon monoxide gas is removed, but with a small amount of the gas present the combination is quite firm. When so combined, moreover, the pigment cannot combine with oxygen itself; so a person poisoned with carbon monoxide is almost as badly off as if he had lost all his blood. The heart pumps valiantly, blood vessels constrict, the chest bellows work at a furious speed; but, though plenty of oxygen is in the air of the lungs and a river of blood gushes past it, the body cells are soon asphyxiated and the person dies.

Hemoglobin, then, is an ingenious chemical product of evolution which greatly multiplies the capacity of the circulating blood to carry oxygen and, more indirectly, carbon dioxide as well. You will hardly be surprised that plants or animals which lack it (except for insects, which have an entirely different device and deliver air itself directly to the body cells) are quite unable to carry on life activities at the speed and intensity possible for those which do possess a blood pigment. They simply cannot get oxygen to their cells in sufficient amounts to support a high rate of metabolism.

THE RED CELLS OF THE BLOOD. The red blood cell (erythrocyte) loses its nucleus in the course of maturing and becomes an almost inert sack of hemoglobin. With minimal metabolism it could hardly survive long, and the average length of life is only one to three months. Old ones are continuously being destroyed and correspondingly new ones being formed—at the rate of some ten million each second!

Life history. The red cells are formed, of all places, in any bone marrow kept warm. Certain large cells anchored along the walls of the blood capillaries or sinuses in the marrow continue to divide and produce smaller cells, which contain nuclei and no hemoglobin. During the further development of these small cells, hemoglobin appears, the nucleus is lost, and finally a new disc-like erythrocyte floats on in the circulat-

ing blood. The young red cell continues its circular travels until old and ready to disintegrate. Then it is torn apart in the swirling blood or, when drifting slowly through the sinuses in the liver or spleen, it (or its fragments) sticks to the wall of one of the endothelial cells in the vessel lining.

These are special cells, often called reticulo-endothelial cells, which occur in small numbers throughout the body but

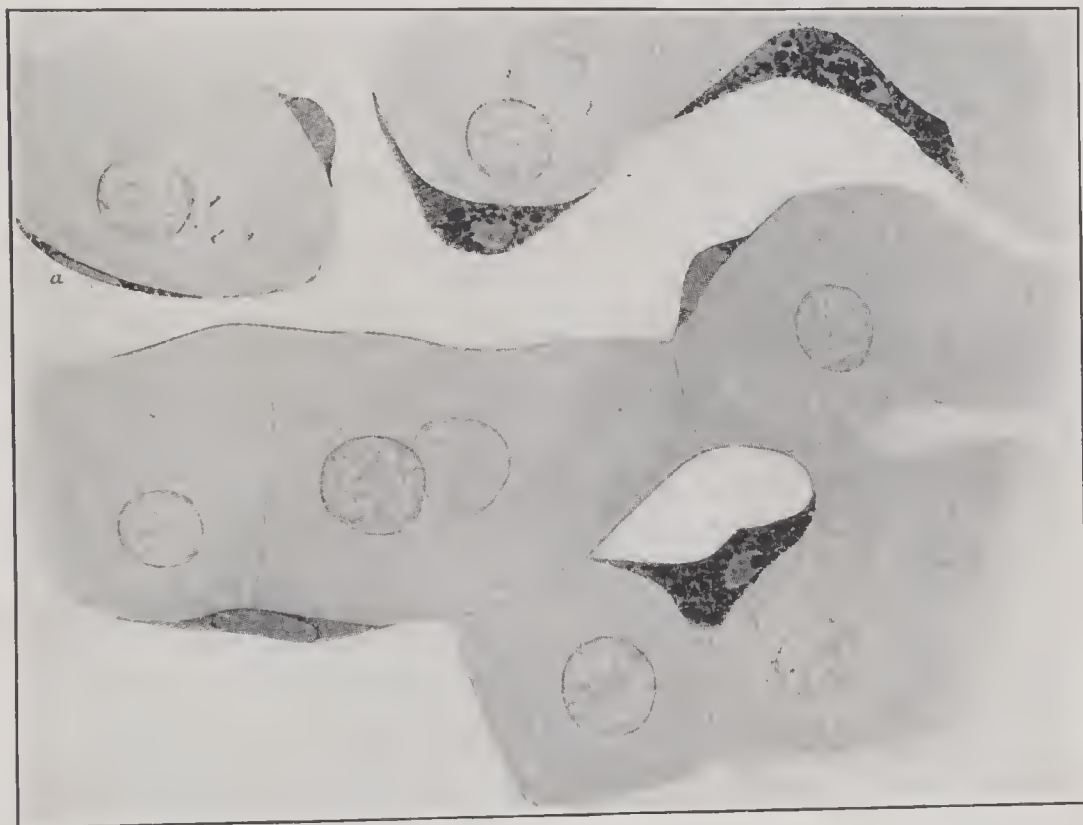


FIG. 64. The reticulo-endothelial cells lining the blood sinusoids of the liver and of the spleen phagocytize solid particles and debris floating in the blood, including old red cells to be destroyed. In this figure these cells are shown, on the surfaces of large liver cells, filled with carbon particles which were injected into the blood and which they have taken out. Similar phagocytic cells in lymph nodes are important in taking up and destroying bacteria. (See Fig. 76.) (After Kupfer. From Downey's *Handbook of Hematology*, Paul B. Hoeber, Inc.)

are especially prevalent in these two organs. Like the white cells which float in the blood, they are able to push out extensions of their protoplasm, pseudopods, which surround and finally engulf particles lying on their surface. This process of cell eating, or phagocytosis, is applied to the stuck erythrocyte (we do not know what causes old but not young red cells to thus adhere), which is completely swallowed by the reticulo-endothelial cell and then digested.

We are concerned mainly with the hemoglobin. This complex molecule is built of a protein, the globin, and coloring substance, heme. Heme is a special molecule with many atoms of carbon and nitrogen arranged in a ring and with one atom of iron set in its center. During its digestion, the protein part is split easily into soluble amino acids, which are used by the phagocyte or diffuse into the blood plasma; but the heme is not so easily disposed of. The iron atom becomes separated as insoluble iron oxide, so that in time the reticulo-endothelial cell is filled with rust spots. The pigment part of the molecule is changed chemically to other closely related pigments, red and green and yellow and brown, and is finally secreted from the other surface of the cells into very fine ducts in the liver, the bile ducts.

The color of bile is thus due to pigments which originated from hemoglobin. From the liver they flow through the larger bile ducts, often with a temporary pause in the gall bladder, to reach the intestine. Some are again absorbed into the blood and, on being excreted, give the urine its yellow color. But most remains in the intestine, is further changed chemically to the brown form and colors the feces. It is in fact possible, by studying the amount of bile pigment secreted from the liver, to estimate the rate at which hemoglobin is destroyed in the body, and therefore the number of erythrocytes which disappear each day.

Has it already occurred to you that you have actually seen hemoglobin turning into bile pigments? When small blood vessels are torn, erythrocytes push into the tissue, say in or under the skin, and a bruise results. These cells cannot get back into circulation but are gradually destroyed locally by the few reticulo-endothelial cells on hand or arriving from the blood. And you have certainly watched the panchromatic display during the weeks that a "black" eye changed from bright red through dull red to green and brown and yellow before finally becoming normal.

Of all the constituents of the destroyed hemoglobin, only the iron remains inert in its living sarcophagus. Now it is no great problem for the blood-forming cells in the marrow to

build fresh globin nor to make the carbon and nitrogen ring of the heme molecule. But certainly no cell can make an iron atom out of some other element. Iron is needed for new hemoglobin, and the average diet contains little of it indeed. Obviously the iron left in the cells of the liver must get back to the blood-forming cells of the bone marrow. But this is not simple, for the iron oxide particles are insoluble and, if dumped back into the blood stream, would probably clog the vessels. Match your wits with the "wisdom" of your body, for the best solution of this difficulty. Ready? Here is your body's answer: When a reticulo-endothelial cell becomes well filled with iron rust it breaks loose from its mooring (usually with the aid of a cell division) and floats off in the blood stream like a freight barge laden with ore! The cargo of iron duly reaches the marrow factory, ready for use in building more hemoglobin for more erythrocytes.

One last point about red-cell production. When formation is interfered with (or destruction increased) anemia results. The most striking example is the disease, pernicious anemia, in which the number of erythrocytes in the blood may fall below one-fourth of the normal value. It is well under ten years since the cause and treatment of this previously fatal disease were discovered. (Three more Nobel prizes on this basis.) For normal red-cell formation an accessory chemical substance is necessary. This is formed from food protein in the course of digestion in the stomach, and is then stored in the liver pending use. Pernicious anemia patients lack acid and proper enzymes in their gastric juice and fail to produce this anti-anemic substance. By feeding them large amounts of normal liver, or of a substance prepared from it, or even by improving their own digestion by adding the missing acid and special enzymes, these patients are kept well.

Control of formation. Finally, how is the number of red cells kept constant? Building and tearing down obviously must keep accurate pace with each other. Do you think this is a simple matter of having once set the speeds of both processes to be equal? If so, how is it that, a week or two

after losing a third or more of his total blood in a severe hemorrhage, a person again has a perfectly normal blood-cell count? Some regulation of erythrocyte production (and perhaps of destruction also, not by hemorrhage but by cell rupture) must occur, then, and the next question would automatically be about the mechanisms responsible. You should, by now, have learned enough of body devices to know what to look for.

The supreme function of the red cells is to carry oxygen; if they become too few or fail to function, insufficient oxygen reaches the tissues, including, of course, the cells of the bone marrow itself. If, then, a deficient oxygen supply to the marrow cells somehow stimulates them to more active red-cell formation, the regulatory control is complete and automatic. Here is a clue to the investigator, indicating the direction of his search—an hypothesis suggesting which experiments to perform. Let us keep animals with a sufficiently low oxygen supply, so that their blood is never fully oxygenated, and see if their erythrocytes gradually increase. We must know how to make a blood count, of course, but this is really very simple—hundreds a day are made in any hospital, and you can soon learn to determine that there are, say, 5 million per cubic millimeter of blood, within 100,000. The experiment is soon done, and the results are as expected. In fact, nature is performing this experiment all the time and we need only observe its results. People living in mountain villages regularly have higher blood counts than those living at sea level; and when a person leaves his Chicago home for a sojourn at Denver his blood count steadily rises until it is like that of the regular residents. The body, then, is fairly consistent in the efficient mechanisms it uses, and we gain confidence in our ability to guess ahead into the still unknown.

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CHAPTER VIII

FOODS AND WASTES

Oxygen is but slightly soluble in water; hence the necessity of the complex hemoglobin mechanism. Were ordinary foods water-soluble, our digestive system could be dispensed with, for its primary duty is to break down complex insoluble molecules into simpler ones able to dissolve in body fluids and diffuse across the membrane barriers of tissue cells. Plants have no need of an alimentary canal since the substances they require from their surroundings are already soluble.

THE DIGESTIVE SYSTEM. The passage through which aliment progresses, in all vertebrates and many invertebrates, is indeed a canal; from mouth to anus it is continuous and completely walled off—by epithelial, muscular, and other coats—from the true “insides” of the body.

To be sure, there are many side branches, such as the ducts which empty into the main passage, but these also end blindly against the walls of the glandular cells. Thus, opening into the mouth cavity are the ducts of three pairs of salivary glands; into the stomach, the multitudinous fine openings of test-tube-like glands buried in the mucous lining; in the upper small intestine, the duodenum, are similar openings of glands in its wall and the large pancreatic and bile ducts entering together. The esophagus or gullet, the small intestine below the duodenum, and the large intestine or colon have no special glands emptying into them; but their lining mucosa, as that of the entire digestive tract, contains numerous cells scattered about its surface which secrete the slippery moist mucus that helps solid particles slide along.

Besides the many glands, there are the various muscular layers, noted earlier, responsible for grinding, churning, and peristaltic movements. Further, since the digested food must ultimately be absorbed through the wall of the intestine, its surface is increased by various devices. As you know, the small intestine is built as a long, narrow, highly coiled tube—

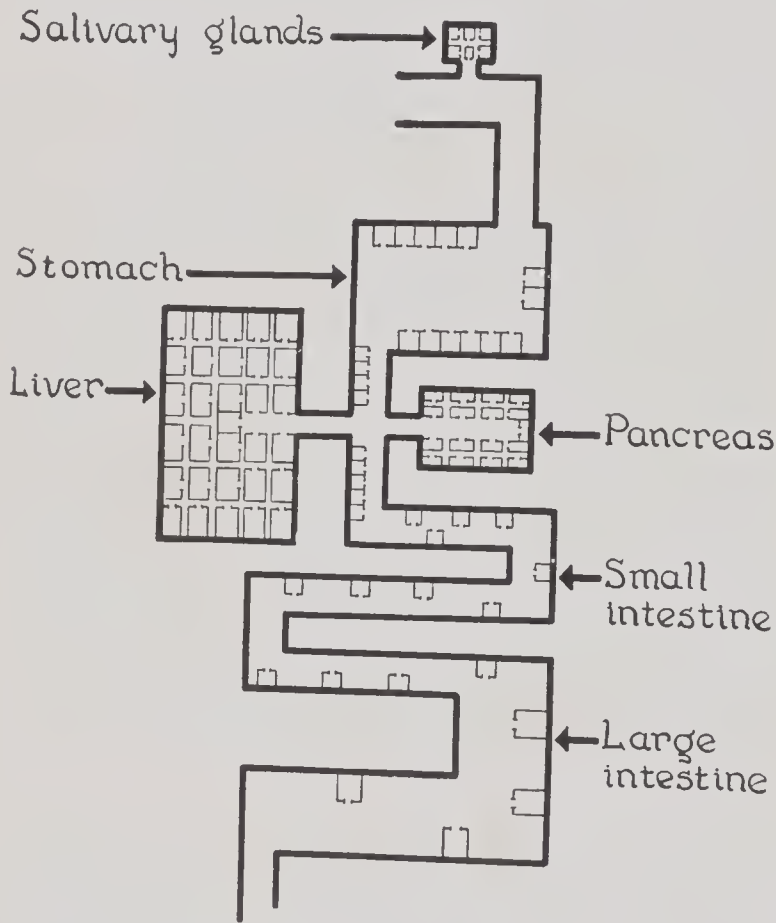


FIG. 65. The cavity or lumen of the alimentary canal, and of all the glands emptying into it, forms a continuous passage to the outside of the body. (Drawn by E. M.)

actually 32 feet in the adult. The mucous membrane, in turn, is folded and pleated to further increase its area—in tripe you have seen this folding in the hog's stomach, where it is only moderate. Finally, each fold is literally studded with microscopic club-like projections, the villi, which again greatly multiply the absorbing surface and which, by intermittent contractions, help to absorb the food and to "milk" it into blood or lymph.

Three major properties of the digestive system, then, contribute to the digestion and absorption of food: The solid and insoluble particles are broken down mechanically with the aid of muscles and, far more important, chemically with the

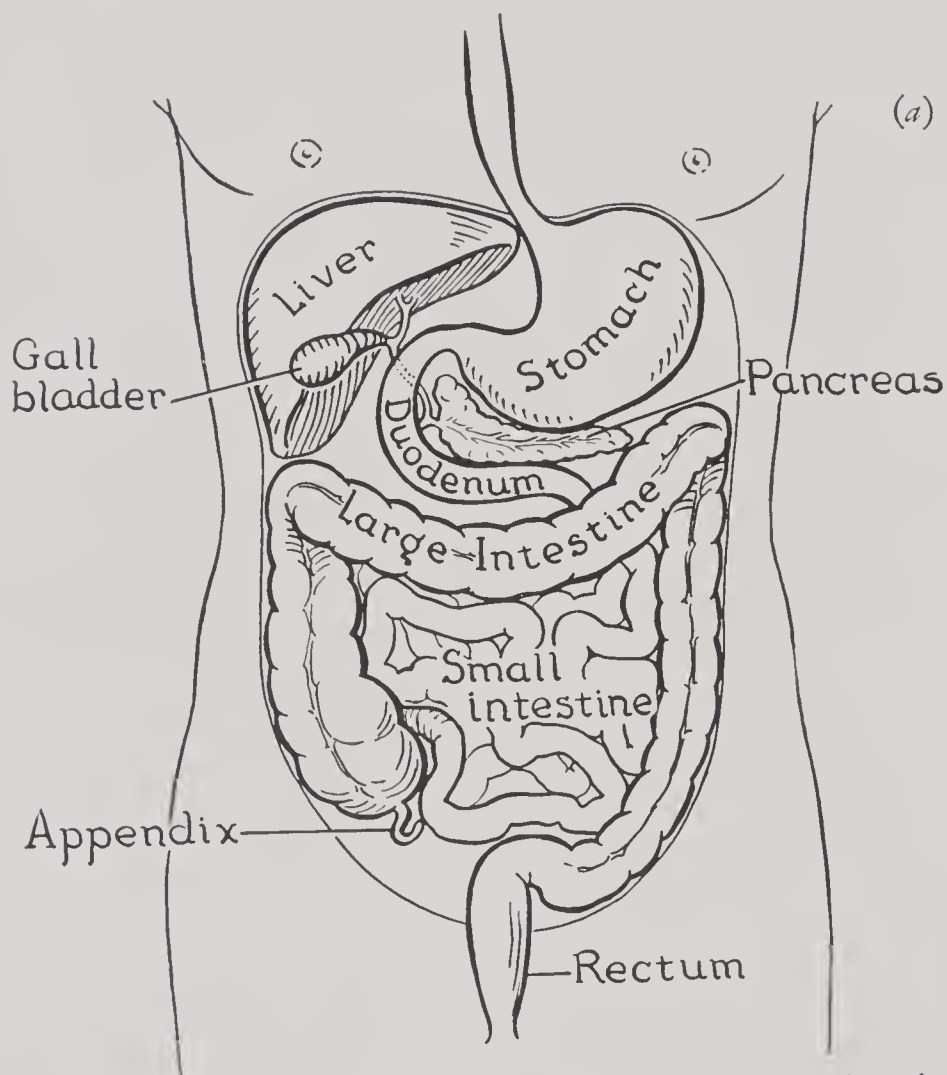
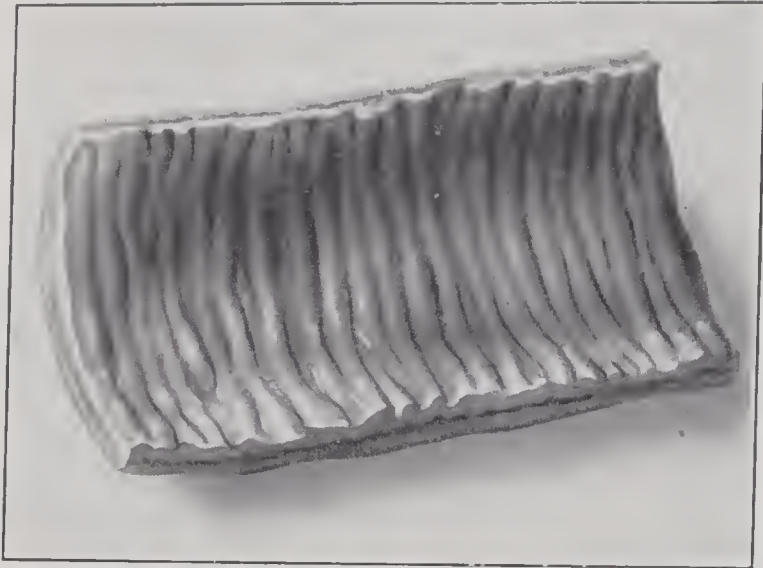


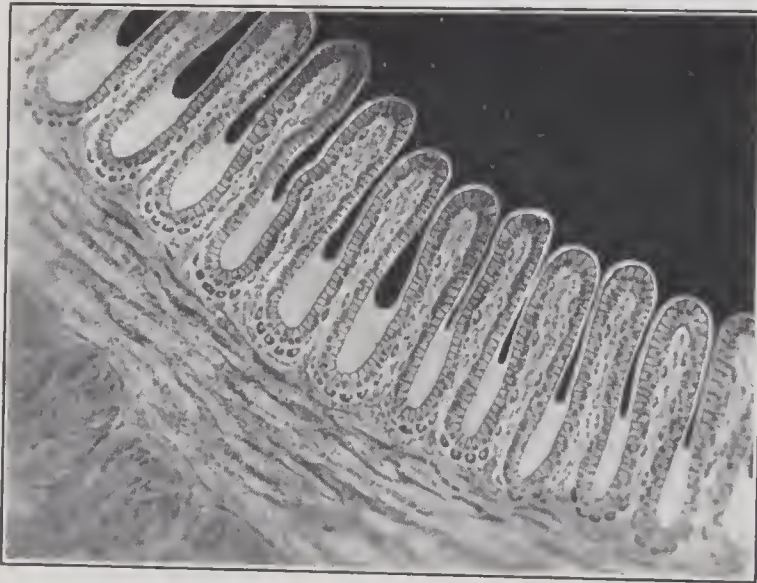
FIG. 66. (a) Diagram of the digestive system, showing the long and much coiled intestine. The mucous membrane of the intestine is further increased in surface by elaborate folding (b); this is indicated in cross section in (c). Finally the entire surface of each fold is pushed up into a mass of villi, shown in the photomicrograph (d). (Figure 66 a and b drawn by E. M., c and d from the film, *The Digestive System*, by Carlson.)

aid of secretions, and the dissolved end products are then absorbed through the enormous surface of the intestinal walls.

MECHANICAL DIGESTION. The movements of digestion and the nerves which control them we have met several times.



(b)



(c)

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(d)

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FIG. 66 (Continued).

Swallowing. Chewing is performed by striated muscles of tongue and jaw which are under voluntary control, as are those of the hand. The complex process of swallowing and the difficulties introduced by the crossing of the digestive and respiratory passages, we have also seen; now we can trace further the mass or bolus of food, tossed by the tongue against the back of the pharynx and left in the esophagus. As one response of the reflex of swallowing, a single powerful peristaltic wave is set up in the esophagus. This depends entirely on efferent impulses along many fine branches of the vagus nerve; for if the esophagus itself is cut the wave still continues in perfect time along both portions of the tube, whereas if some vagus branches are sectioned the denervated portion of the gullet fails to contract.

Often, however, the food bolus is not carried all the way to the stomach by this first rush. When you feel something "stuck in the throat" you keep tossing back droplets of saliva to start a series of swallows and repeated peristaltic waves to help carry on the bothersome lump. Incidentally, if you think you can swallow, except when the back wall of the pharynx is stimulated by some object, try the old trick of chewing dry crackers. When your tongue is unable to toss material against the pharynx, no act of willing will enable you to make a swallowing movement.

But even without additional swallowing, the stranded bolus will find its way to the stomach with the aid of a second type of peristalsis. Wherever it rests it distends the esophagus, which sets up afferent impulses from stretch receptors and leads to a reflex contraction of the wall immediately above. The bolus is slowly forced onward and the same reflex is repeated from each new position, the contraction remaining efficiently behind the mass rather than running blindly ahead, as did the first type of peristalsis. The opening from esophagus to stomach is guarded by a thickened ring of smooth muscle, a sphincter which is normally closed. The same nerve impulses which make the esophagus contract make the sphincter relax, so permitting food to enter the stomach.

Stomach contractions. The stomach, you will recall, progressively relaxes as the meal drops in. It is only a few seconds from mouth to stomach, but there digestion begins in earnest



FIG. 67. X-ray photograph showing strong contraction waves in the stomach. The stomach is visible by virtue of barium sulfate recently swallowed in some milk. Bits of intestine are similarly visible in the lower part of the picture because they contain barium sulfate swallowed earlier. The backbone can be seen to the left, indicated by the heavy white bar. (Courtesy Roentgenology Staff, Billings Hospital.)

and it will be four or five hours before your dinner has left this organ. Contractions start near the right end of the stomach, where the powerful pyloric sphincter normally blocks it from

the duodenum. Circular constrictions, as in typical peristalsis, travel slowly towards the pylorus and help stir the contents. As digestion proceeds, the waves originate further and further to the left and become ever more powerful until the entire stomach wall, from esophagus to pylorus, is swept by deep constrictions. The early waves, though pushing food against the pyloric sphincter, do not force the gate; but later the sphincter opens, first a little and then more generously, as each wave presses the stomach contents against it and the liquid chyme (as the contents are now called) makes its way into the duodenum.

The stomach is finally empty but the contractions become still more vigorous. These powerful spasms cause the afferent impulses which arouse the sensation of hunger. This is simply proved by swallowing a soft rubber balloon connected to a manometer. The contraction waves of the stomach squeeze the balloon, raise the pressure in the manometer, and write their presence on a moving drum (Fig. 68). The subject signals whenever he feels a pang of hunger; and the signals and contractions are found to appear together.

Control of the pylorus. Now how does the pylorus "know" when digestion has gone far enough for it to pass the chyme through? One point is obvious: A greater pressure is exerted on the sphincter by the later powerful contractions than by the early feeble ones. But this is not enough. In pyloric spasm, a disease seen mostly in young babies, the pylorus stubbornly refuses to relax; and it is quite powerful enough to resist the most vigorous gastric contractions. You have recalled, perhaps, the ability of parasympathetic nerves to relax the gut sphincters, and this is indeed another controlling factor. But the main regulation is chemical.

The gastric secretion contains a high concentration of hydrochloric acid, and only when this juice has made the entire stomach contents distinctly acid is gastric digestion approaching completion. If, then, sufficient acid in the stomach made the pylorus relax, a proper control would exist. (Actually, this depends on reflexes in nerve plexuses in the stomach

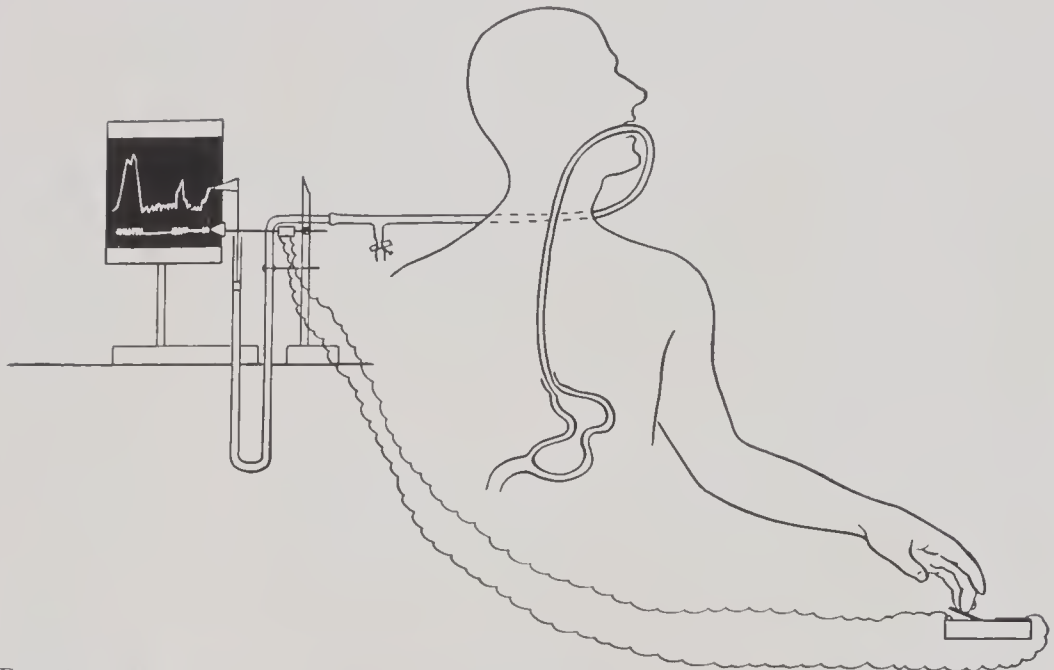


FIG. 68a. Arrangement for recording stomach contractions by a manometer connected through a thin rubber tube to a soft rubber balloon, which has been swallowed and then inflated while in the stomach. (Drawn by P. McC.)

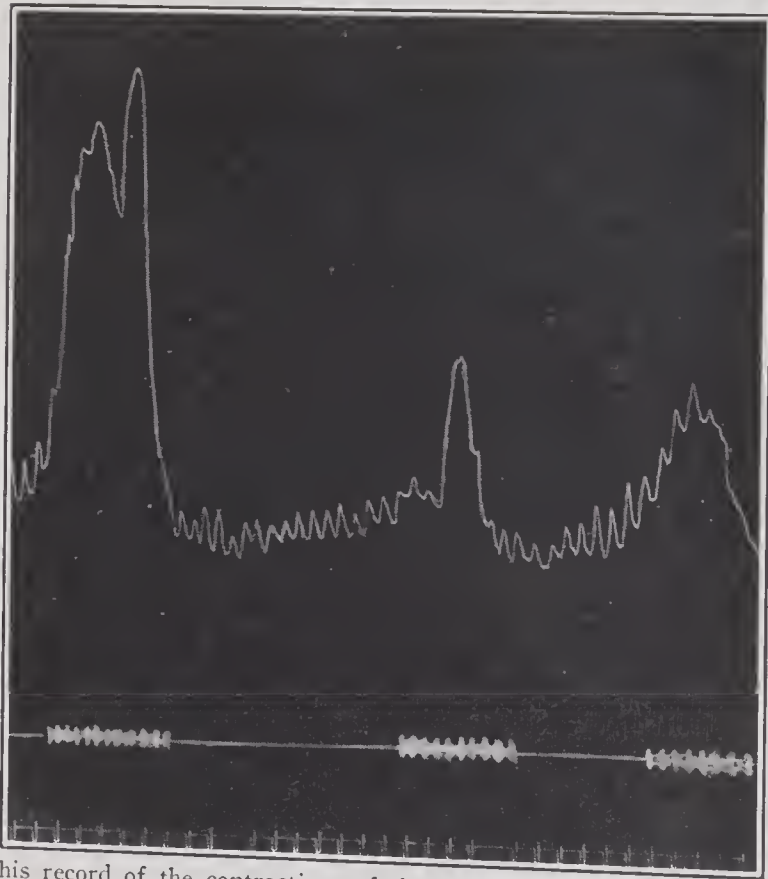


FIG. 68b. This record of the contractions of the stomach shows a sharp rise of pressure with each contraction wave. The small, fairly regular waves are due to the rhythmic squeezing of the stomach by the diaphragm as breathing proceeds. The subject tapped a key connected to the signal magnet, writing the upper horizontal line, while he was feeling a hunger pang and without watching the record of his stomach contractions. It is obvious that each contraction wave produced a hunger sensation. The lower line shows time in five-second intervals.

wall.) The experiment to prove this is ridiculously simple. Remove the stomach of a freshly killed animal, hold the open esophageal end up, and pour in a liquid. When an alkaline fluid is introduced the pylorus remains shut and the stomach fills, but an acid runs right out through it.

“But,” you should now ask, “once the chyme has become acid why does not the pylorus remain open and allow all the gastric contents to pour into the duodenum?” You may also think of the answer: When the duodenal contents, normally alkaline, become acid the pylorus is stimulated to clamp down again. After one good dash of acid chyme, therefore, the sphincter holds until the duodenal contents have been neutralized, by the bile and pancreatic juice. (Actually the response is more complex than indicated, especially when neural elements are not depressed by anesthesia.)

Peristalsis. In the duodenum the chyme is well mixed with the new juices by a series of constrictions, which develop at short intervals along the duodenum but do not travel. When this “rhythmic segmentation” has served its end, the usual peristalsis begins and the chyme is slowly moved on. The main movements of the remaining small intestine are repeated waves of gentle onward peristalsis, and another three or more hours elapse while the contents are moved toward the large intestine. During this time intestinal digestion is completed and the great bulk of food absorbed.

In the colon, similar movements, though partly in a backward direction, continue even longer. Water is absorbed until the chyme gradually solidifies into fecal masses as it approaches the rectum. Finally the rectum fills, its distended walls send messages indicating the need to defecate, there result a voluntary relaxation of the outer anal sphincter and contraction of the abdominal walls and an involuntary reflex relaxation of the internal sphincter and contraction of the wall of the rectum; and the indigestible roughage from the food swallowed some eighteen hours earlier, plus bodies of bacteria which grew in the colon, plus broken-down epithelial cells, plus other rubbish, is finally eliminated. If opportunity offers, watch the passage

of a "barium meal," along the digestive system, and see these movements in a way no description can duplicate.



FIG. 69. This X-ray photograph shows the rectum, large intestine, and lower part of the small intestine, made visible with the aid of an enema containing barium sulfate. (Courtesy Roentgenology Staff, Billings Hospital.)

Other movements. The alimentary tract can perform other movements, of protective value or as a result of disease, which are primarily directed to ridding itself of harmful content.

The poor gut has nothing to say about what things our sometimes misguided appetite, or an unhappy accident, dumps into it; but when the insult is too severe it can at least eject much of the offending material. Vomiting is a reflex contraction of the entire stomach, resulting from irritation of its wall or from direct stimulation of the vomiting center in the medulla, through which this reflex acts. It is a complex coordinated act involving, for example, contraction of the abdominal muscles as well as of the stomach; and the stomach contents are sometimes ejected with force.

Irritation in the upper intestine may cause peristalsis to reverse in direction, antiperistalsis, and so lead to vomiting of intestinal contents, including the bitter dark bile. Such backward discharge is especially important when the intestine has become completely obstructed, by getting badly kinked or by a cancer growing in its wall, for then all secretions which form above the blockade must leave through the mouth. Sometimes tremendous amounts of fluid are lost and the resulting dehydration and salt deficiency can alone cause death. More commonly, irritation in the small or large bowel causes a more rapid onward peristalsis or an especially vigorous mass contraction of the entire colon. As a result, the contents reach the rectum when still semi-solid or completely liquid, and are discharged as a diarrhea. Castor oil liberates a strong irritant when partially digested in the intestine, and you know how it acts.

Most people seem more disturbed about inadequate activity of the colon, when they consider themselves constipated, than about its excessive action. In most such cases nothing whatever is wrong, and the taking of cathartics has all too often brought on the digestive ailments they were supposed to avert or remedy. If one's diet contains little "roughage," woody fibers and like indigestible substances, little solid material gets through the alimentary gamut. Medical literature records authentic cases of healthy, hard-working men whose bowels moved less frequently than twice a year!

Another overworked bugaboo, by the way, is "autoin-

toxication." The intestine normally teems with bacteria which produce all sorts of poisons; but these do no harm so long as the gut wall is uninjured. The cells in the mucosa have a remarkable ability of absorbing the nutritous molecules formed by digestion while rejecting the injurious molecules, often closely related chemically, which are formed from them by the bacteria. The real cases of food poisoning are due to infection with strange bacteria, such as that of typhoid fever, or to swallowing the already formed poisons of bacteria, such as that of the botulism bacillus which infects and spoils improperly sterilized canned goods. The accumulation of the ordinary intestinal contents does no harm until, in such conditions as obstruction, they distend and damage the wall of the gut.

CHEMICAL DIGESTION. It is time, now, to repeat the voyage through the alimentary canal with our attention fixed on chemical events. All the gut movements would never suffice to digest food, whereas the alimentary secretions easily do. This was proved over two centuries ago by simple but heroic experiments. Spallenzani swallowed a perforated rigid capsule filled with meat and, after leaving it in his stomach for several hours, hauled it out again on a string. The meat had disappeared. The next step was obviously to obtain gastric juice, which must have done the digesting, add meat to it outside the body, and see if the same process still took place. Stomach contents can easily be sucked out through a rubber tube and, kept warm, are found to digest meat quite as well as within the stomach. Aspirating the stomach is now a routine in the diagnosis of certain stomach troubles. A standard meal of tea and crackers is taken on an empty stomach and at fixed intervals afterwards the stomach is "pumped" to determine the amount and properties of the gastric juice secreted.

Saliva. We had better begin, however, with the salivary glands, for the saliva they secrete not only lubricates the food but has an important digestive action as well. Saliva breaks down starch and other complex sugars to simple soluble ones,

mainly maltose. You can easily test this by utilizing the fact that iodine forms a deep blue with starch, but no color with sugar. Into a cup of dilute "soluble" starch solution pour a teaspoonful of your saliva. Have several drops of tincture of iodine scattered about a plate, and two times a minute add a drop from the cup to a fresh portion of iodine. At first the mixture becomes bright blue, soon red, due to a partially broken-down starch compound, and finally it is colorless. The starch has been digested; and you will note that the solution in the cup is no longer cloudy but perfectly clear. Now repeat, but heat the saliva just to boiling before adding it to the starch. The test will show that the starch remains. Clearly some substance in the saliva, destroyed by heat, is responsible for starch digestion. This is called ptyalin, is a protein and, of course, an enzyme. It is the powerful and specific action of the enzymes in the various digestive juices which is really responsible for breaking down our foods.

Control of salivation. Salivary secretion is controlled through autonomic nerves to these glands. The centers of these nerves, in the medulla, are stimulated by impulses both from the cerebrum and from touch and taste receptors in the mucosa of the mouth. Chewing almost anything, such as wax, leads to an increased secretion of saliva; and many tastes, especially the sour of acids, are even more powerful stimuli. Further, the smell or sight or, when hungry, even the thought of appetizing food can make the mouth "water," as well you know. Stimulation in these cases comes from the cerebrum and depends on past experience.

Fried caterpillars, appetizing to a South American Indian, would strike you as nauseous. At the sight of such a dish, his saliva would flow whereas your stomach would rebel. In both cases, the response is conditioned by the habits of thought and action developed during the individual's experience. "Psychic" secretion of saliva is indeed the phenomenon which led to, and is extensively used in, the study of such "conditioned reflexes." A similar, though less important, "psychic" control of gastric secretion, even of that of the pancreas, is through

the vagus nerve. As we pass down the alimentary tract, however, we find that secretion falls more under chemical and less under nervous control; nerves regulate the formation of saliva, gastric secretion is intermediate, and the liver, pancreas, and duodenum are overwhelmingly controlled by chemicals.

Gastric juice. What does the stomach actually secrete? The remarkably high acidity of gastric juice was proved last century to be due to hydrochloric acid. But any hope that the secret of gastric digestion had thus been exposed was soon shattered; for boiled gastric juice, or a pure hydrochloric acid solution of even higher acidity, has only a trivial digestive capacity compared to the fresh juice. Another enzyme is obviously active here, the pepsin of lay knowledge and one of the half dozen or so which biological chemists have succeeded in crystallizing in the pure state. Pepsin, as indeed probably all the enzymes, is a protein; and its activity is directed against proteins.

You have seen earlier that a protein molecule is built by linking many simple amino acid molecules. There are as many kinds of amino acids as there are letters in the alphabet; and, as letters can be combined in varying sequence and number to give an immeasurable number of different words, so are the proteins formed from amino acids unlimited. But the widely different proteins present in corn or silk, in milk or liver, or in the blood and various tissues of each kind of living organism, all digest down to mixtures of the same amino acids. The gastric juice starts this process but does not complete it; the long protein chain of amino acid beads is broken into shorter strings or even into occasional pairs and triplets but not to the individual units. The dismemberment is completed by the enzymes trypsin, obtained from the pancreas, and erepsin, from the duodenum.

If pepsin digests the proteins, why do the gastric glands trouble to produce free hydrochloric acid? Because pepsin is active only in fairly strong acid solutions. Trypsin, in contrast, is most effective in an alkaline medium, and the pancreatic juice contains large amounts of alkaline sodium carbonate. If

you ask why the body did not devise protein-digesting enzymes which work in neutral solutions, I can say only that there *are* proteolytic enzymes, present in most body cells though not ordinarily secreted, which do just this. An excised bit of tissue kept warm and moist finally liquefies, or autolyzes, under the action of its own proteolytic "cathepsin."

Surely the question is agitating you, "Why does not the stomach digest itself?" The answer is not simple and in part is, "It does." For one thing, the acid and the enzyme are formed by different gland cells, mainly in separate parts of the stomach wall, so active juice is not present until these mix. But the stomach contents are rather effectually separated from the wall by a layer of mucus, continuously renewed and quite resistant to peptic digestion. Further, the epithelium of the stomach, somewhat like that of your lips, is alive and forming new cells to replace the injured and dead ones. And, finally, but little gastric juice and of low acidity is formed except when food is in the stomach to mix with it. When excessive amounts of highly acid gastric juice are secreted, when the blood supply to mucosal cells is impaired, when a sharp lodged food fragment produces maintained injury, or when several conditions act together, then the stomach wall *is* partly digested and gastric ulcer results. One of the approved treatments of this disorder is feeding fats and alkaline salts, which effectively diminish the secretion of acid or neutralize that produced.

Control of stomach secretion. How, next, is the gastric secretion controlled? Partly through nerves, stimulated by impulses from the brain, the "psychic" secretion, or from receptors in the stomach wall. The juice is not poured out promptly after food is swallowed, however, but rather increases steadily in amount and acidity as gastric digestion proceeds. Further, the juice secreted varies with the food taken; it is much greater following meat, mainly protein, than bread, mainly starch, and is very little when the food is largely fat. To study this without allowing swallowed food to mix with the gastric juice, a neat operation has been devised. A portion of the stomach is partly cut away, the cut walls are resewed

so as to close the stomach and make a small pouch, and the free end of this pouch is brought to the surface through the skin. The little pouch acts, after healing, as a model for the whole stomach, and its pure juice is easily collected from the external opening.

We must conclude that meat acts somehow to stimulate gastric secretion, or fat to inhibit it, or perhaps both. Actually,

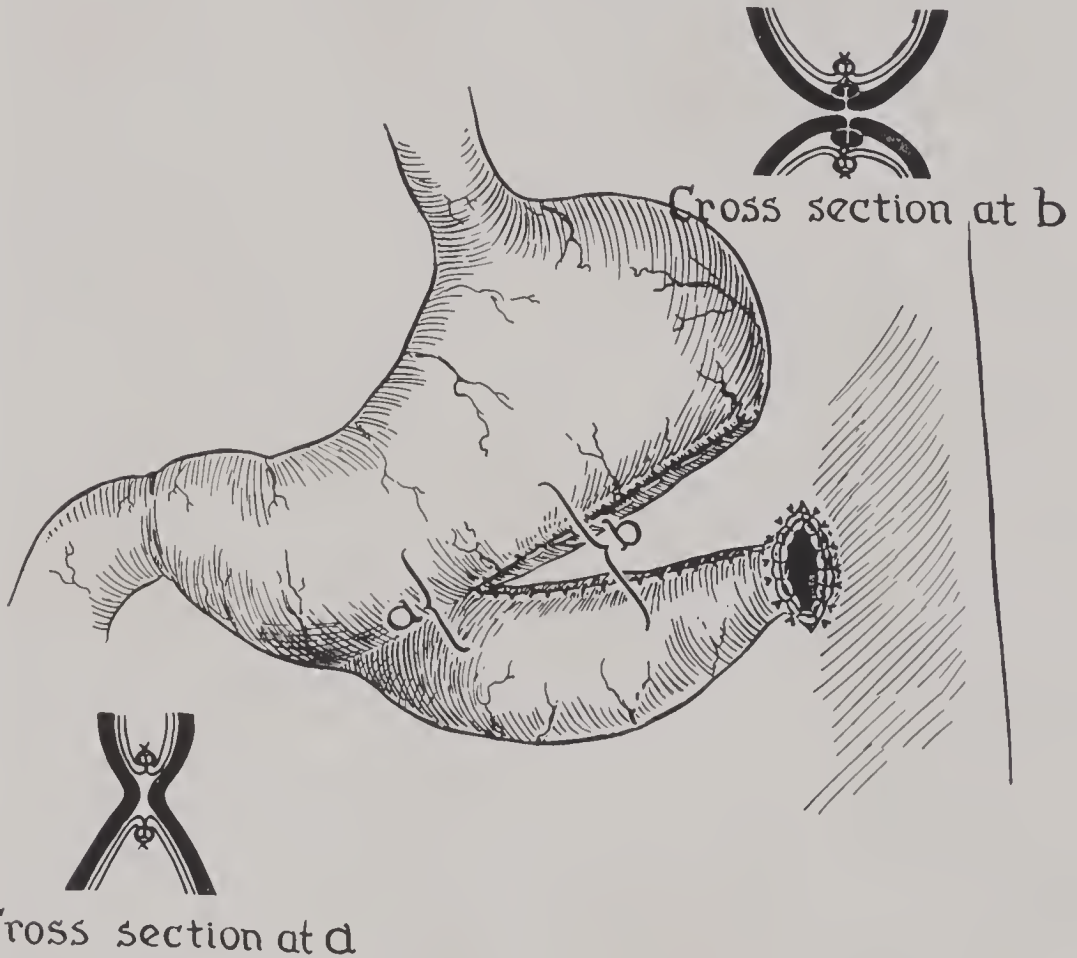


FIG. 70. Diagram of the operation on a stomach to prepare a Pavlov pouch.
(Drawn by E. M.)

meat itself is rather inactive; but peptic digestion liberates from it powerful stimulants to secretion, secretagogues, which enter the blood and excite the gastric glands. Hence the progressive increase in acid juice after meat enters the stomach. This will remind you (Chapter III) of secretin, liberated from the duodenum by acid to stimulate pancreatic secretion; and indeed there is evidence for a similar substance, gastrin, which helps

activate the gastric glands. As to fat, a mixture of fat and protein not merely fails to stimulate secretion but actually tends to inhibit it. There is evidence, though not proof, that fat liberates from the duodenal wall another chemical messenger, *enterogastrone*, which reaches and depresses the stomach.

Pancreatic juice. The pancreatic juice contains several important enzymes and acts upon all the ordinary foodstuffs. Its trypsin reduces the partially broken down proteins left by pepsin to bits of two or three amino acids, their final separation being performed by intestinal erepsin. A starch-splitting enzyme, amyllopsin, complements the work of the salivary ptyalin; steapsin splits fat into soap and glycerin; and other minor enzymes make their various contributions. Actually, the pancreatic juice contains not trypsin but its inactive precursor, trypsinogen. (When active trypsin does accidentally get into the pancreas it proceeds to digest it, a rare cause of death.) This pro-enzyme is changed to trypsin in the duodenum, by a substance (enterokinase) in the intestinal secretion.

There is no special problem about the digestion of proteins or carbohydrates. They soon appear in the water of the chyme as single molecules, or tiny colloidal particles, at whose surfaces enzymes, also in the water, can freely nibble. But the fats are another story, for they do not mix with water and enzymes act very slowly on the large fat droplets. Oil and water do not mix; but in the presence of many organic salts, such as our common soaps, the sodium salts of fatty acids, they form a fine emulsion. In it the oil drops are split to the minute dimensions of colloidal particles, the exposed surface is enormously increased, and the emulsified fat can digest at a reasonable velocity.

Bile and the gall bladder. The main function of bile is to supply just such emulsifying "soaps," the bile salts, to the intestinal contents. When the bile duct into the duodenum is blocked, as by a gall stone, the victim can get along on a fat-free diet, but any fat is not digested and passes on into the stool. (The bile pigments, of course, are also blocked from the in-

testine so these fatty stools are a dirty clay color. The dammed-back bile finally gets into the blood and tissues and, among other things, tinges skin and eyeballs with the yellow of jaundice.)

Bile is formed in the liver and flows from it to the duodenum through the bile duct. There is an unusual feature of this passage in that it connects by a side branch to a good-sized sac, the gall bladder. Since there is a sort of sphincter at the intestinal opening of the bile duct, it seems reasonable to regard the gall bladder as a reservoir for bile not needed in the gut. But when we find further that 300 cubic centimeters of bile may be secreted during a meal, whereas the bladder can hold only about 50 cubic centimeters, this explanation is hardly satisfying. True, water is absorbed through the gall-bladder wall so that the important bile solids become highly concentrated. (This of course contributes to the formation of gall stones.) Even so, simple storage can hardly account for the presence of the gall bladder, and, on that basis, why are there not similar bladders for the pancreatic and other ducts?

More probably, the gall bladder has a duty in controlling bile secretion. Secretin and other substances absorbed from the gut can make the liver secrete; but by far the most powerful of such agents or cholagogues are the bile salts themselves. When bile enters the intestine its salts emulsify the fats and then, with the fatty soaps, are absorbed into the blood stream. The bile salts are carried around the circulation, again reach the liver cells, stimulate them to further activity, and are themselves re-excreted, thus completing a "cycle." But how is such a cycle to be started or stopped?

Let us consider a meal just entering the duodenum. Nerves in the gut wall may be stimulated and reflexly cause the gall bladder to empty its stored bile into the intestine. Perhaps more important is the liberation, especially in the presence of fat, of a hormone, cholecystikinin, which contracts the gall bladder. In either event, concentrated bile salts are dumped into the duodenum, some promptly absorbed and carried to the liver, and the secreting machinery set in motion. Con-

versely, when digestion is completed the duct sphincter closes, but bile salts are still being absorbed and circulated and maintain the liver secretion. The bile now being formed, however, is diverted into the gall bladder, the amount in gut and blood stream falls, and liver secretion stops. The gall bladder, then, is useful not for its stored bile as such but because this small quantity "primes the pump" and starts a much larger flow.

A B S O R P T I O N. Absorption of the fully digested food products is itself not simple, and far more than diffusion is involved. Glucose, for example, is combined with phosphate to get through the cells quickly and is then freed, while the digested fat is recombined in the mucosal cells. (A hormone from the adrenal cortex is concerned in these processes.) The fat then passes into the lymph vessels, which empty at a distance into the veins. And we have seen that amino acids are carefully picked out from their toxic relatives.

The simplest proof that living mucosal cells actively pass substances across them is offered by an experiment which you may be able to try. A piece of intestinal mucosa, say from a frog, is placed as a membrane between two curved glass tubes, which together form a vertical U with the membrane at the middle of the bottom. Both tubes are now filled with one solution, say blood plasma, and left for some hours. The fluid level falls on the side of the membrane which normally faces the intestinal cavity and rises on the side normally facing the blood stream. Clearly the mucosa "pumps" substances across it, with the aid of energy liberated in its own metabolism.

T H E L I V E R. The liver does much more than secrete bile. We have seen its importance in controlling the blood sugar; it produces more profound changes in the molecules of amino acids, glycerin, and fatty acids which pass from the intestine directly to it. The glycerin may be changed to sugar; the fatty acids are shorn of some hydrogen, combined with phosphorus, broken into shorter molecules, or even changed

in part to sugar; the amino acids are deprived of nitrogen, which forms first ammonia and then urea, and the remaining molecule is changed perhaps to sugar; and sugar itself is built into glycogen or burned or in turn changed into fat or even, with ammonia added, into an amino acid. In other words, besides its many other duties, the liver is a great chemical laboratory in which all sorts of transformations are produced in the absorbed foodstuffs, in accordance with the body's needs.

FOOD REQUIREMENTS. We cannot do reasonable justice to the great field of metabolism and nutrition—after all, the whole of respiration, digestion, and excretion is really accessory to the actual chemical manipulation of food substances in the living cells—for this huge subject is dependent upon chemical knowledge. Our examination of the chemistry of muscular contraction and of the control of blood sugar, and the indicated activities of the liver, should give you, however, some idea of what is involved. But we can look at what comes into the body and at how the soluble wastes are removed in the urine.

Calories. The need for water and salts, and some roughage, in an adequate diet has been touched upon; but the main food requirement is fuel to supply needed energy. Fats, sugars, and proteins can all be oxidized in your body, but they do not yield the same amount of energy or heat. One gram of fat, completely oxidized to carbon dioxide and water, yields 9.3 large calories (i.e., the heat produced would raise the temperature of one liter of water 9.3° C.), whereas the same weight of sugar or protein yields only 4.1. Obviously, as a stored fuel reserve fat is over twice as efficient as either of the other substances; so it is not surprising that when we eat food in excess of the needs of the moment we “lay down fat.” This serves as a hoard against hard times, and a person with a proper fat deposit can starve over a month and be none the worse for it.

We have earlier considered the energy needs, in terms of basal metabolism plus the variable extra requirement of muscular work, and have seen how hunger helps control the food

intake to meet these requirements. Since, however, the body can interchange all three foodstuffs, does the proportion of each eaten matter so long as sufficient total calories are supplied? We should hardly have guessed the recent discovery, that in the absence of a small amount of fat in the diet serious disease results. But we should certainly anticipate that no amount of fat and sugar could long maintain life in the complete absence of protein. These two substances lack nitrogen and can never alone be built into proteins or the many other nitrogen-containing molecules of protoplasm. Of course this would make any growth impossible; and, since survival itself represents a balance between the continued breakdown of body substances, catabolism, and their equally continuous building up, anabolism, closely related to growth, even the adult body would go to pieces from nitrogen starvation.

Nitrogen. Our diet, then, must include protein; at least enough so that the body remains in nitrogen balance, receiving as much of this element in food as is lost in wastes. But foods rich in protein, as meats and dairy products, are relatively expensive—to produce them, animals eat much larger amounts of vegetable food than they yield in body parts or products—so it is of great practical importance to determine the needed quantity of protein. The answer cannot be obtained by measuring the nitrogen in the urine during a period of starvation and then feeding the same amount of nitrogen as protein. Unfortunately, when protein is fed the nitrogen excreted also increases. Actually a considerable fraction of the food nitrogen appears in the urine, even of a starved animal; and, more, taking protein food somehow stimulates body metabolism (known as the specific dynamic action) so that catabolism is greater and even more food is required.

But nitrogen equilibrium can be attained, granting enough supplementary fat and sugar to supply fuel needs, over a wide range of protein administration. The upper limit is unimportant, for when excess protein is fed the carbon part of the molecule is largely stored as fat, and the nitrogen, separated in the liver and changed to urea, is thrown out in the urine to

strike the balance. The minimum protein per day on which men have maintained nitrogen equilibrium for months or years is about fifteen grams, the amount in the white of one or two eggs. But man the world over, eating without thought of the problems of nutrition, and despite great variation in culinary habits, settles down to a diet containing about eighty grams. Even the experimenter who remained healthy and energetic for six years on a minimum protein intake promptly returned to the usual one on ending his experiment. The conclusion seems to be that, while man can manage nicely on one-sixth of the protein he ordinarily consumes, he prefers the greater amount. It has been suggested, but without good evidence, that this high intake is an evil of civilization and that the extra work demanded of the kidneys in eliminating the surplus nitrogen is a cause of increasingly prevalent chronic nephritis.

Amino acids. Obviously, any necessary chemical elements must ultimately be obtained in food. But it might also be true that certain particular compounds are beyond the body's capacity of manufacture and must likewise be obtained from outside sources. Animals, for example, cannot make sugar from carbon dioxide and water but must obtain it directly or indirectly from plants which can. In this case, much energy from sunlight is built into the product, so animals which cannot capture this energy can hardly turn the trick. More surprising is the inability of animals to manufacture a number of absolutely essential molecules, from closely related ones which they can make. Thus, your body can build, from available sources of nitrogen, over half the known amino acids of protein, but the other ten are beyond its power of synthesis and must be taken in food. Since some vegetable proteins contain little of one or another essential amino acid, a diet of one or a few vegetables, even though supplying enough nitrogen, may still be inadequate. A more extensive mixture, especially one including animal proteins, is likely to be satisfactory. Nutritional needs, and probably metabolic prowess, differ considerably from one

species to another; compare, for example, the normal diets of herbivores and carnivores. Man is a good deal of both.

Vitamins. Besides the essential amino acids, other special organic compounds are vital to the body's welfare, particularly the vitamins, the alphabet in our nutritious soup. Lack of vitamin A leads to a type of eye disease; of B₁, to the convulsions and paralyzes of beriberi; of B₂ to B₄, to the weight loss, skin inflammation, and anemia of pellagra, to mention only one horror; of C, to the bleeding gums and joints of scurvy; of D, to the soft and deformed bones of rickets; of E, to sterility and muscular weakness; and of K (I can't tell you what happened to all the missing letters; some vitamins are not required by human beings), to decreased blood coagulability and to hemorrhage. But perhaps the steady din in your years about all sorts of vitamin-containing products—via radio, newspapers, advertising pamphlets, and lectures—has left you slightly fed up with the subject. In any event, we cannot examine further the many new and significant facts about vitamins which lie behind such parlor conversation.

EXCRETION BY THE KIDNEY. We must still, however, follow the excretion of metabolic wastes. Aside from the carbon dioxide (and water) lost through the lungs and unimportant quantities of salts, urea, etc., which leave the body in sweat and tears and intestinal juice, the wastes are secreted by the kidney. These glands are built of over two million like units which perform the same function. Each nephron, as the unit is called, begins near the outer surface of the kidney as a closely tangled tuft of capillaries, the glomerulus, which protrudes into and nearly fills an otherwise open cavity. The endothelial membrane lining the cavity is pushed in on itself by the glomerulus, which it also covers, the whole resembling a thumb thrust into a hollow ball. This ball is not closed, however, for, at a point roughly opposite the glomerulus, the membrane opens into a long, highly coiled tubule with walls of cuboidal epithelial cells. This convoluted tubule is separated into proximal and distal portions by a segment which forms

one long straight loop, down and up again; and the far ends of the many distal tubules join together, one after another, until all empty into the ureter, which carries the urine on to the urinary bladder. The capillaries in the glomerulus, arising

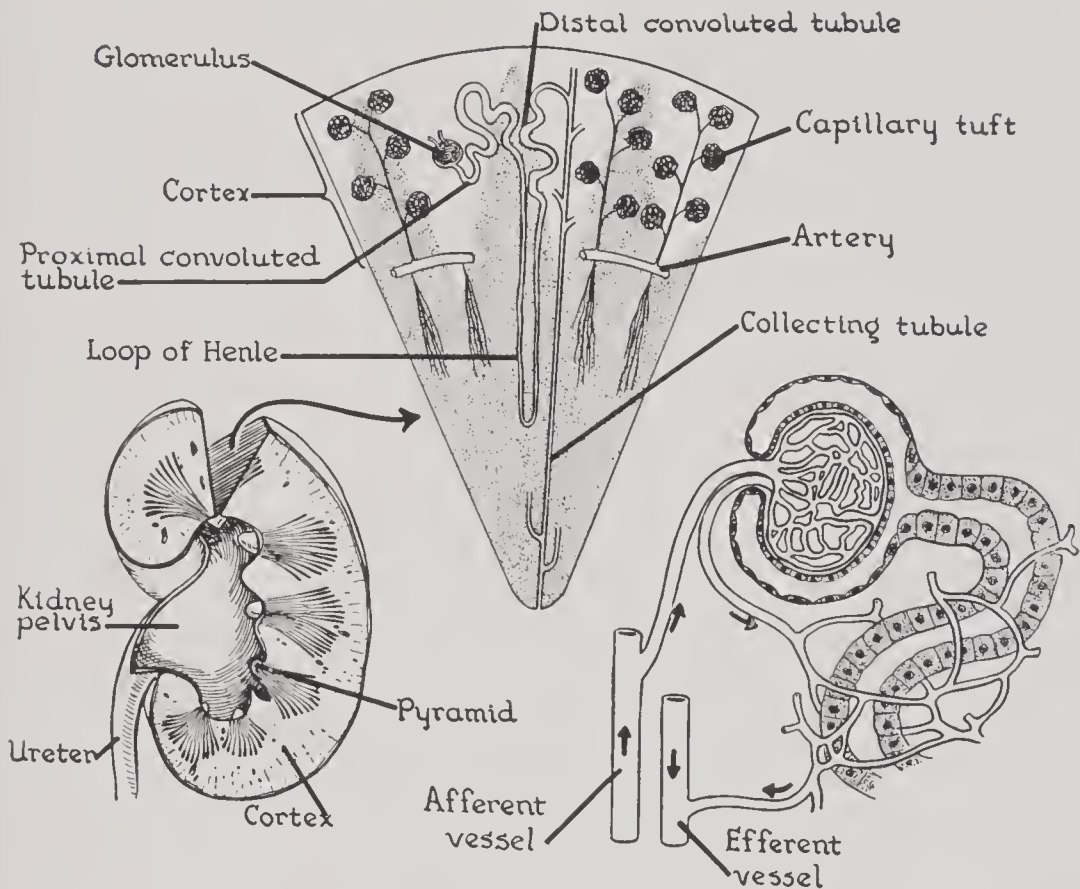


FIG. 71. This diagram of the kidney (left) shows the general arrangement of cortex and pyramids. Above is a sector enlarged, with a single nephron (with its glomerulus, proximal convoluted tubule, long loop, and distal convoluted tubule) drawn in the center. On the sides are shown the blood vessels forming capillary tufts in many glomeruli, and their leaf-like arrangement. On the right, a single glomerulus and the beginning of its tubule are drawn in greater enlargement and the details of their blood supply are indicated. Note that the arteriole entering the capillary tuft of the glomerulus is larger than the vessel leaving (suggesting that the volume of blood leaving the glomerulus is less than that entering), and that the outflow vessel again breaks up into capillaries around the tubule before finally joining others to form regular veins. (Drawn by E. M.)

from the renal artery, do not immediately empty into the renal vein after joining together but rather redivide to form new capillaries which are distributed about the tubule cells.

Obviously, material might pass from the blood into the lumen of the nephron in two ways, through the glomerulus

and through the tubules. Fluid entering the cavity through one source might even be reabsorbed through another. Actually, these all happen. Comparing the composition of blood and of urine tells which substances are not excreted at all and which are excreted in greatly increased concentration; but not where in the nephron the job was done. Many ingenious experiments were devised to gain such information and finally a courageous frontal attack was successful. The nephron is, of course, microscopic, a large glomerulus is hardly 0.2 millimeter in diameter, and all are buried in the kidney, deep in the abdomen. Yet, in the living animal, experimenters have directed fine glass capillary tubes through the membrane into the space around the glomerulus, collected from it minute amounts of the fluid formed by the glomerulus, and measured quantitatively the substances present!

Filtration. The glomerulus looks suspiciously like a device for filtering blood plasma, and these experiments proved that it does just this. The blood in the capillaries is under moderate pressure, the fluid outside is at a lower one; and the water and dissolved substances, except for proteins and other colloids, simply filter out through the permeable wall. This glomerular fluid, then, contains water, sugar, salts, urea, etc., in the same proportions as plasma and far from those of the urine; these proportions must be changed by the tubule cells, and this means that they must do work. Filtration in the glomerulus depends on the pressure generated by the heart, but further change depends on the kidney cells and should be abolished when their metabolism is blocked. When poisoned with cyanide, the kidney produces a greatly increased amount of very dilute urine, its usual concentrating action being lost.

Reabsorption. The tubules, then, must reabsorb water from the filtrate and return it to the blood in the capillaries surrounding them. Further, sugar is present in urine from the poisoned kidney, as in blood and in glomerular fluid, but there is none in normal urine. The tubules, therefore, must reabsorb all the sugar as well as much of the water from the glomerular filtrate, as it slowly passes through them. Actually,

about 120 cubic centimeters of fluid is filtered from the glomeruli per minute—a rate which would empty all the body water in a couple of hours—but 99 per cent of the water is reabsorbed in the tubules, especially in the long loop and with the aid of a pituitary hormone. The water diabetes mentioned earlier results from defective reabsorption. The remaining 1 per cent of fluid, something over 1 cubic centimeter per minute, accounts for the 1,500 cubic centimeters of urine formed per day. The various salts which filtered out of the blood may be mostly reabsorbed or may pass on and appear in the urine concentrated many times owing to the absorption of water. Still more, the concentration of urea and related nitrogenous wastes in the urine may be over one hundred times as great as in the plasma.

Secretion. Such increases cannot easily be accounted for merely by the reabsorption of water, and they suggest that these substances have been actively secreted by the tubule cells. That these cells can, in fact, secrete into the lumen has been shown in several ways. For one thing, certain fish kidneys completely lack glomeruli, so that filtration is impossible, yet produce a perfectly good urine—obviously by tubular secretion. Further, even with glomeruli, filtration stops when the blood pressure is lowered sufficiently, but urine still forms. In fact, dyes injected into the blood of animals in this condition can be seen to pass through the cells of the tubule into its lumen.

The urine, then, is formed by a delicate chemical jockeying, with filtration, reabsorption, and secretion all helping. We know pretty well where these processes occur. But how they occur, except for the mechanical filtration, is still a mystery.* The action of our mechanical effector, muscle, is reasonably well understood; when we have gained similar insight into the

* The kidney has other important duties in relation to the circulation. If the glomeruli are abnormal, in nephritis, plasma protein is passed through and the decreased protein osmotic pressure in the plasma helps to cause water to seep into tissues and contributes to the dropsy which results. The normal kidney, further, seems to liberate into the blood a vasodilator substance while a kidney with imperfect circulation liberates a constrictor substance (renin), and so can bring on a chronic high blood pressure.

mechanisms whereby the chemical effectors—the gland cells which take in substances on one surface and from another surface give off different ones, or the same ones in different concentrations—carry on secretion or absorption, we shall have made a great stride in unraveling the mechanisms of living organisms.

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CHAPTER IX

PROTECTION AND PRODUCTION

SPECIFIC SYNTHESIS. The last three chapters have considered the organs and organ systems which are primarily concerned with maintenance of the dynamic equilibrium of the body—that balanced series of chemical or metabolic events which, like a flame, maintains itself by a continuous inflow of food and energy and outflow of wastes. Respiration, digestion, excretion, circulation, and the circulating fluids are devoted overwhelmingly to these problems. The behavior of the whole organism in its environment, as well as that of its parts in the body's internal environment, and the coordinating and integrating mechanisms—the devices, in short, devoted to adaptive amplification—have been considered in the first chapters, and will receive further attention in the final one. Indeed, we have met every major structure of the body; but we have failed to examine many of them or their functions from some important viewpoints. Now we must pick up loose threads. Particularly we must think in terms of that last great attribute we share with all living things, the ability to perform specific synthesis, which is seen most simply as growth.

MECHANICAL BARRIERS. Let us approach indirectly by considering a group of activities—intermediate between maintaining the body's status quo and building new cells and substances—which are concerned with protection against injury and disease. Take, first, the purely mechanical barriers your body has erected.

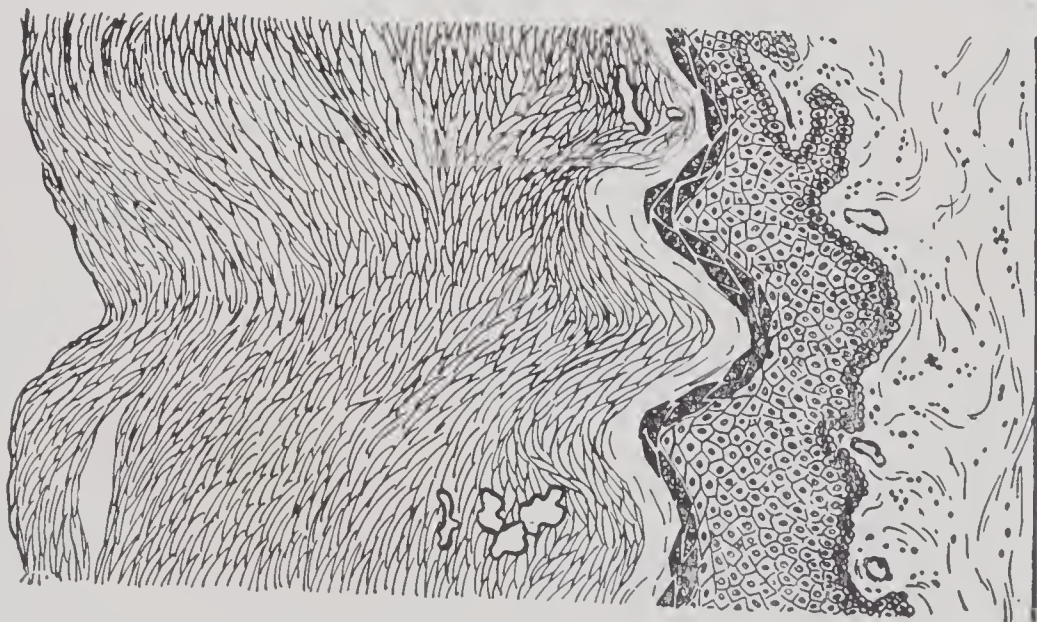
Epithelium. The body's outer surface is covered by a heavy epithelium, thick and tough with piled-up layers of

dead horny cells continuously renewed from living ones at the base as the outermost dried-up plates are worn away. To appreciate its protective power recall how all sorts of liquids and even gases, which produce pain and irritation in an open cut, leave the intact skin unaffected. The thinner epithelial linings of the passages which open into the body—mouth, nose, rectum and anus, urethra, vagina, etc.—also afford protection against mechanical or chemical insult, though not so much as does the more exposed skin. They do, however, like the skin, offer a nearly impregnable barrier against bacteria, which successfully invade the tissues proper only when this barrier has been broken.

Reflexes. Further, many accessory mechanical devices protect the body from injury. Reflexes of all sorts help to eliminate the offending stimulus: the pulling away by flexion of a burned finger; the explosive cough when an irritant enters the respiratory passages; the vomiting or diarrhea which expels irritants from the intestinal tract; the peristaltic contractions of the ureter which attempt to force out a lodged kidney stone, and which are accompanied by severe spasms of pain; even the cramp-like contractions of the uterus, which act to expel menstrual clots from its cavity, are familiar examples. Another mechanical help, earlier encountered, is the sticky ciliated membrane of the nose and bronchi which catches foreign material and whips it out.

The omentum. A somewhat different device is the omentum, a large extra apron-like fold of the peritoneum, hanging more or less from the stomach. The peritoneum, like the pleura in the chest, covers the abdominal viscera and the inner surface of the abdominal wall to give one large cavity folded in on itself. When irritation is set up in this cavity the omentum somehow finds its way to the spot and, adhering to the injured region, forms a barrier against spread of the trouble. Thus, the omentum becomes stuck to the peritoneal covering of the stomach wall at the base of an eroding ulcer and gives both support to the weakened wall and a partition to help restrain the stomach contents should the ulcer finally

FIG. 72. These three diagrams of body epithelium give some idea of the resistance which such cell layers offer to penetration by chemicals or bacteria. The middle drawing shows a cross section through ordinary skin, as on the back; that on the right shows the thinner mucous membrane within the mouth; and that on the left shows the greatly thickened skin of the sole of the foot, which has become hypertrophied by pressure and stimulation from walking barefoot. (Drawn by E. M.)



perforate. The omentum similarly packs itself about an inflamed appendix and often walls off the pus, released when the appendix ruptures, which would otherwise spread through the abdomen and lead to a fatal peritonitis. (After infection, or even the irritation of surgical procedures, the peritoneal surfaces may become permanently attached, causing occasional trouble as adhesions.)

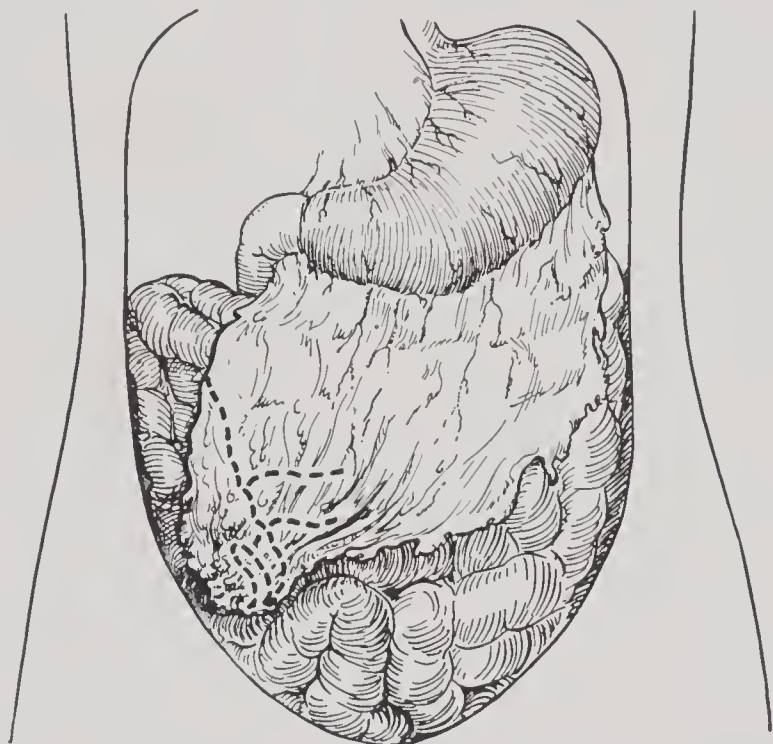


FIG. 73. The omentum, that apron of peritoneum hanging from the stomach over the front of the abdominal viscera, is shown here after having found its way to and wrapped itself about an inflamed appendix. (Drawn by E. M.)

CELLULAR DEFENSE. The mechanical barriers do, however, break down and admit trouble. The microbes are by far the most important offenders, for they alone, being living, grow and multiply; so that if even a few penetrate the first defense, large numbers would soon be present unless restrained. Two other mechanisms, cellular and chemical defenders, are continuously being called upon to protect your well-being. The cellular protectors are the phagocytes, or devouring cells, exemplified by the reticulo-endothelial cells. Resting phagocytes are scattered in various degrees of profusion throughout the tissues. In the presence of irritants, as bacteria

or the chemicals they produce, these large cells become active, move about by pseudopods, and even undergo repeated cell division.

The phagocytes. These macrophages move towards the source of the chemicals which stimulate them; much as a plant turns towards light or an amoeba migrates towards food, their crawling movements are controlled by the intensity of the outside condition. These cells are "positively chemotactic"; they travel towards ever more concentrated solutions of the stimulating chemical, and so reach the seat of the trouble. The gathering of pre-existing macrophages and the local production of new ones mobilize a powerful army of phagocytes to ingest and digest the offending bacteria.

Even before the macrophages lumber into the field, however, the smaller and more mobile microphages of the blood become engaged. These are the white blood cells, including the lymphocytes and the granulocytes. The former are produced in the lymph nodes and are continuously lost by migrating out through the intestinal mucosa. They seem quite inactive in the blood stream but, on leaving it, may grow into typical macrophages, and are thus an additional source of these fighters. The granulocytes, like the red cells formed in the bone marrow, show some amoeboid motion even in the blood. When stagnated in dilated capillaries, and particularly when stimulated by chemicals diffusing in from an injured region, they squeeze in large numbers between the endothelial cells of the capillary and swarm about the point of infection or injury. Their travel also is directed by chemicals and by electrical currents which always flow between normal and injured cells. Fortunately the production of new granulocytes is increased during a continued infection. The doctor, suspecting such a condition, makes daily blood counts and, if a white cell count of 15,000 to 60,000 develops, the diagnosis is pretty certain.

The microphages likewise engulf bacteria or other foreign bodies; and with only a few such invaders the microscopic struggle in your body is completed while you remain oblivious

to it. But the outcome is not always so satisfactory. Sometimes an unusually large number of bacteria enters the tissue; or the bacteria may be especially virulent and grow rapidly, spread extensively, and form large amounts of powerful toxins; or there may be few or feeble phagocytic cells to meet them, owing to pre-existing unhealthiness. (Certain drugs popularly used to relieve pain are dangerous because their repeated administration decreases the blood leucocytes.) In such cases the conflict is more extensive and prolonged, and you have a boil or



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FIG. 74. This diagram shows leucocytes stuck to the wall of a capillary in an infected bit of tissue (bacteria indicated by dots) and beginning to push their way between the cells of the capillary endothelium to reach the bacteria. (From the film, *Body Defenses against Disease*, by Cannon.)

carbuncle or appendicitis or tonsilitis or, in general, an “inflammation” somewhere in your body.

Inflammation. Recall the last time you tore the cuticle around your nail and developed an infection. Probably it remained a small affair and ended as a tiny boil which came to a minute head, drained a droplet of pus, and healed. The inflamed part of the finger was red and hot, two excellent indications that more blood was flowing through it, that its arterioles and capillaries had dilated. Evidently the irritant chemicals, as does carbon dioxide normally, relax the smooth muscle and stretch the endothelium of blood vessels. Further,

the stretched and thinned lining, subjected to increased capillary blood pressure within, allows more plasma to filter through. This leads to local edema and to swelling—a third symptom of inflammation. Finally, of course, the infected region was painful and unusually sensitive to touch, owing to the increased pressure and to the action of irritating bacterial poisons on receptors and nerve fibers.

You probably regarded the inflammation as a nuisance. Yet, had the same infection occurred without the inflammation,

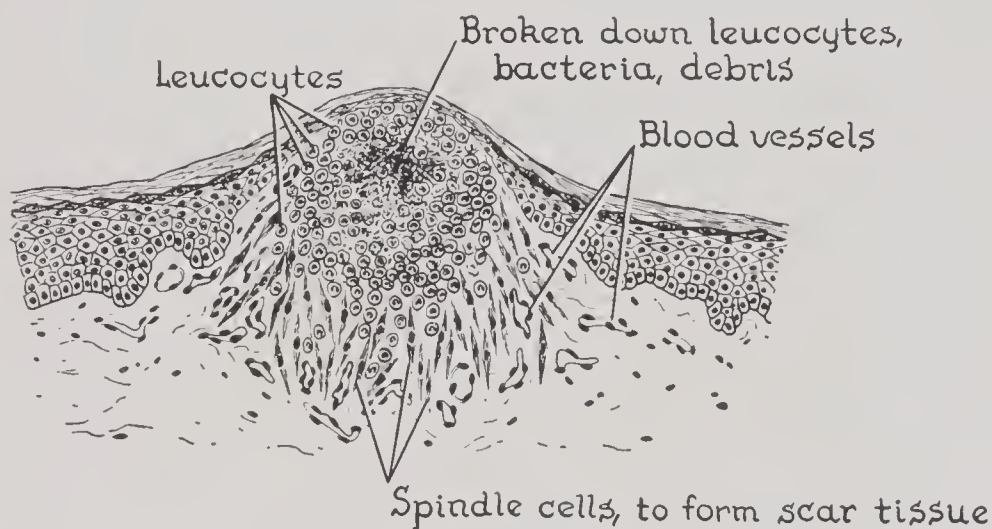


FIG. 75. This diagram of a well-developed boil shows the broken-down bacteria and phagocytes forming pus in the center and a surrounding wall of newly formed fibroblasts. The boil is about to "point" through the skin and, if undisturbed, will discharge the pus from the body and heal from below by further changes in the wall around it. (Drawn by E. M.)

you would probably not be here to read this book. The increased blood supply mobilized at the danger point great numbers of phagocytes and also brought large amounts of the protective chemicals, the antibodies, still to be considered. In the infected tissue occurs the mortal strife between phagocytes, which swallow and digest the bacteria, and bacterial poisons, which kill and help autolyze the phagocytes and other cells. Casualties are heavy on both sides; and broken-down cells accumulate in the already watery tissues to form thick, white, semi-fluid pus. As pus develops in the center, many macrophages have formed a more or less continuous encircling wall; and by the time the boil points and opens, the

pus has been segregated and the bacteria killed. You see, however, how dangerous it is to fuss with a boil not yet "ripe." This merely breaks down the forming wall and disperses still living bacteria through previously uninfected tissues. At best, the whole defense process must then be repeated on a wider scale; at worst, the bacteria are carried away in blood or lymph and lead to more serious, even fatal, consequences.

The macrophages also undertake the repair following inflammation, as after a wound and temporary blood clot. They elongate, perhaps divide some more, are gradually transformed into connective tissue cells, and weave about themselves the usual connective tissue fibers. (Similar changes bring about healing of such chronic infections as tuberculosis. The "tubercles" in a healed consumptive are scattered grains of tough connective tissue.) Finally, the epidermal cells divide and grow to meet their fellows. Across the opening, a complete skin layer is re-established, and, except for a slight depressed scar, no monument remains to the heroic action.

The lymphatics. If conditions were less favorable you did not overcome the infection so lightly; some bacteria were carried away, from the point of inoculation, in the blood or, more likely, in the lymph. When bacteria reach the blood, directly or through the lymphatic system, a case of "blood poisoning" or septicemia develops. Many of them are phagocytized by the reticulo-endothelial cells, lining capillary sinuses in the liver and elsewhere; a majority is destroyed by antibodies, partly with the help of granulocytes; and, of course, if some manage to survive and multiply, death results. This fortunately is the rare outcome; we have each undoubtedly had bacteria in the blood stream a number of times.

More frequently, bacteria enter and grow in the lymph vessels and reach the lymph glands. Red painful streaks, extending up an arm or leg from an infected digit, are infected lymph vessels. They end in lymph glands which, when similarly inflamed, become swollen, hard, and tender lumps under the skin. These lymph nodes are a type of filter plant through which the lymph trickles along narrow twisted passages lined

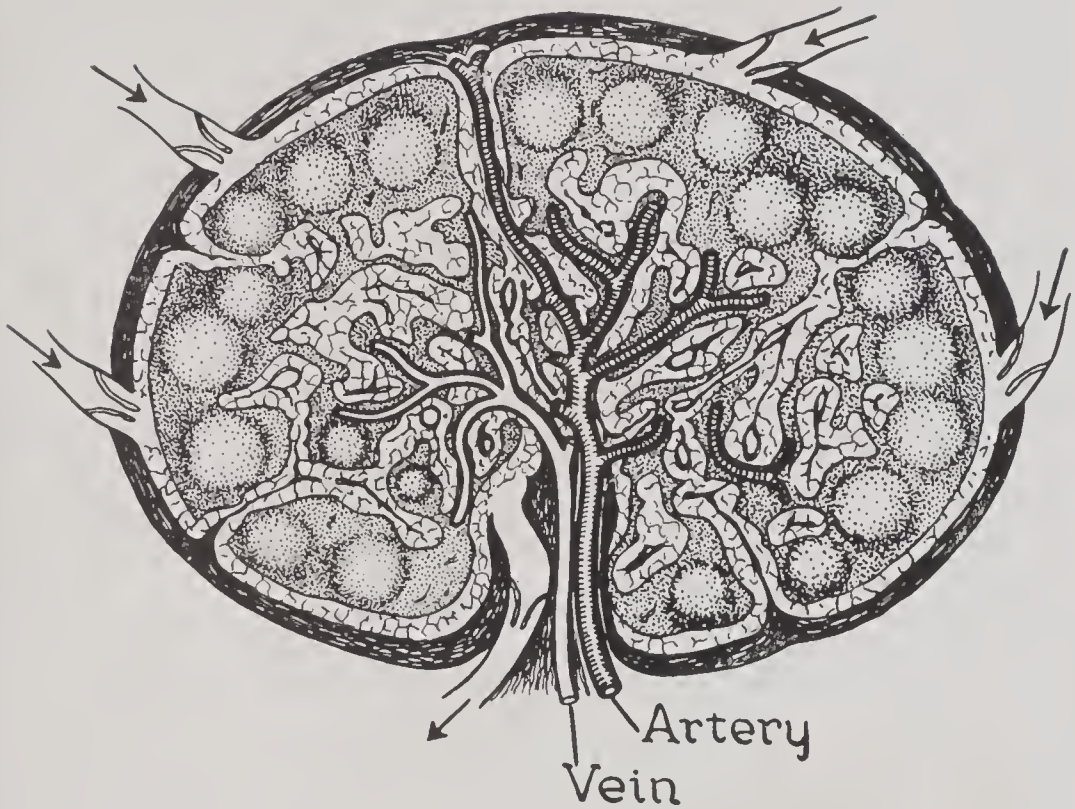
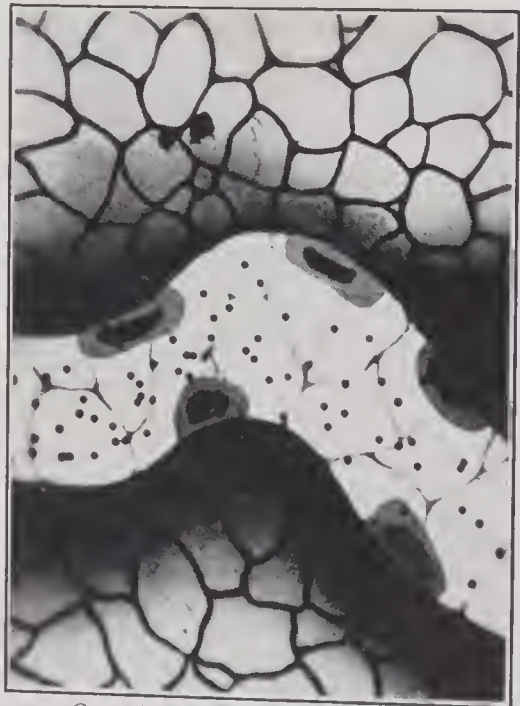


FIG. 76. This cross section of a lymph node (above) shows lymph vessels entering into the periphery, following a tortuous path through the body of the node, and leaving from one side. Lining these channels are numerous phagocytic cells (seen in the enlargement right) which take up and destroy bacteria passing through. The numerous roundish areas near the edge of the node show where lymphocytes are being formed. (Drawing above by E. M. Picture at right from the film, *Body Defenses against Disease*, by Cannon.)



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with phagocytic cells. Here is a formidable gamut to be run by the wandering bacteria; and only rarely, when great numbers of virulent organisms extensively damage the nodes, do the invaders get past. Even so, other nodes lie before them, and beyond these are the special defenses in the blood itself.



FIG. 77. Lymphatic channels are shown in the left thigh and in the abdomen, mainly along the arteries, as the thin curvy lines; and the lymph glands, especially seen in the groin, are the heavier spots through which these lines run. (Drawn by P. McC.)

Lymph nodes, as you would expect, are located in greatest number around those passages and organs which offer the most favorable "portal of entry" to bacteria. There are few, if any, directly under the thick skin, but some are scattered along the larger lymph vessels from it, particularly on the flexor sides of joints, such as the knee and elbow hollows, the armpit, and

the groin. Many more surround the nose and mouth, and the familiar tonsils are just an especially large and complex pair of them. Others surround the bronchial tree and, of course, lie in and around the intestine and the peritoneum.

CHEMICAL DEFENSE. It is easy to say that phagocytes digest bacteria; but bacterial bodies have essentially the same composition as those of other plants or animals, and an entire gastro-intestinal system is devoted to digesting these foods. The crucial agents, to be sure, are the enzymes, and it follows that phagocytic cells must also possess or produce appropriate digestive enzymes within their tiny bodies. But remember, further, that most enzymes are extremely particular as to the substances upon which they act and that each kind of bacterium differs from every other, particularly in its proteins. Perhaps, then, the phagocytes possess a modest assortment of moderately specific enzymes but can develop, in addition, a large quantity of enzymes highly specific for the particular bacteria upon which they are acting.

Autocatalysis. It may seem like pulling itself up by its bootstraps for a cell, which must digest protein B, to synthesize within itself a protein-B-digesting enzyme; yet this is only a case of autocatalysis.* When you come right down to it, is

* Many chemical reactions are extremely slow but can be accelerated by the presence of other materials which do not themselves enter into the reaction and are not themselves used up or altered in the process. For instance, even iron will not combine with oxygen to form rust unless traces of water are present. This phenomenon of assisting or promoting a reaction by the mere presence of a specific third material or agent is known as catalysis and agents which act in this way are known as catalysts. Heat, light, and acids are other examples of common catalysts. Enzymes are a class of catalysts which are produced by living cells, contain protein, and are extraordinarily efficient and specific in their action.

But certain kinds of catalysts accelerate reactions which, among other things, produce more of the catalyst itself. These are known as autocatalysts. They are especially important because the amount of the catalytic agent progressively increases and therefore the speed of the main reaction increases very rapidly. An explosion is a common example of such a reaction. In this case heat is the original accelerator. It sets in process a chemical change, which produces more heat which causes still more rapid reaction, which in turn gives still more heat. The reaction is autocatalytic and, in this case, is so speeded as to become explosive.

not the whole process of growth and reproduction an example of this very thing? One staphylococcus put into a solution of chemicals which do not otherwise react causes chemical changes—its own metabolism—which lead to the production, among other things, of more staphylococci. The proteins and enzymes of the first bacterium catalyze the formation of more of these same substances in its descendants; and, with the increase in number of bacteria, and amount of catalysts, the rate of further growth is likewise accelerated.

Antibodies. In any event, chemical substances which destroy the infecting organism soon appear in the infected individual. These “antibodies” are produced by the reticulo-endothelial cells, presumably as a consequence of the digesting activities of the cells, and the excess formed seeps out from the phagocytes into plasma and lymph. The concentration of antibodies in plasma can suddenly be increased by stimulating the reticulo-endothelial cells; for example, by injecting into the blood carbon particles for them to phagocytize. But now we must learn something of the antibodies themselves.

If the blood or serum of a normal person is mixed with typhoid bacilli nothing much happens, but when the same procedure is carried out with serum from a person sick with typhoid fever, or recovered from this disease, the results are very different. First, the bacteria can be seen to clump, or agglutinate; then the individuals in the clump become progressively blurred; and finally they dissolve completely. Or white blood cells may be seen to approach and avidly phagocytize the clumps. Presumably, some substances are present in the second serum which are absent from the first; and we can test for their enzyme nature by heating, the usual procedure for destroying proteins and inactivating enzymes. The heated typhoid serum loses all its special activities.

In the typhoid serum, then, are enzyme-like antibodies which act against typhoid bacilli. It is doubtful today that more than one antibody is involved (though other substances cooperate with it); but, when these phenomena were being discovered, antibodies could be tested for only by their action,

and many names were given. The one which clumps bacteria was called agglutinin; that which dissolves them, bacteriolysin; and the one which aids the leukocytes in engulfing them, opsonin (meaning caterer). Antibodies acting upon bacterial or other proteins, such as hemolysins which dissolve blood cells, or precipitins which coagulate dissolved proteins, have been similarly identified. These, in turn, have proved tremendously useful as tests for various substances and in the

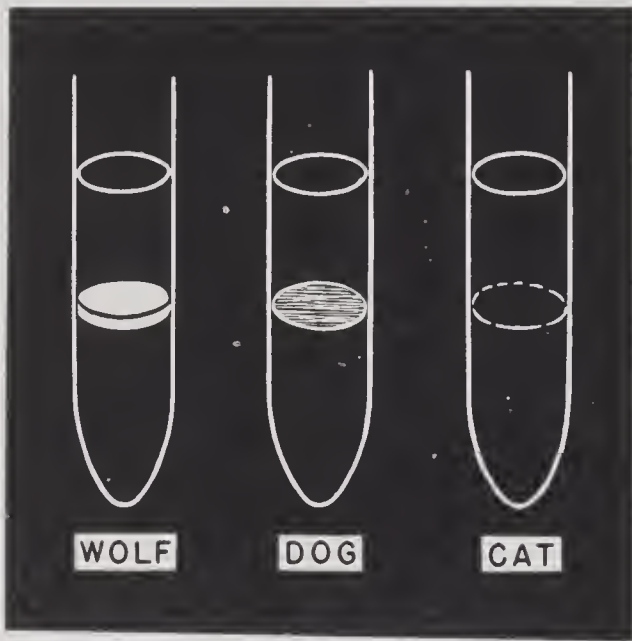


FIG. 78. The serum of a rabbit "immunized" with wolf blood will cause a heavy precipitate of the proteins of wolf plasma when this plasma is added to the rabbit serum in a test tube. The chemically similar proteins of dog blood may give a very faint precipitate, but the quite different ones of cat's blood do not react at all. (From Gerard's *Unresting Cells*, by permission of the publishers, Harper and Brothers.)

diagnosis of disease; for the antibody produced under the influence of some one kind of protein acts specifically on this kind and will not attack others. Even closely related ones are only slightly acted upon.

Blood tests. The blood of a typhoid-fever patient, for example, will agglutinate typhoid bacilli but not the related dysentery bacilli, and conversely for blood from a dysentery patient. An agglutination test, therefore, frequently aids in the diagnosis of these and like diseases. Similarly, blood serum from a rabbit previously injected with horse plasma will pre-

precipitate the proteins of horse plasma but not those of the cow. Such serum, then, when tested with an extract from hash, easily indicates any adulteration with horse meat. This same rabbit serum, containing horse-protein precipitins, will, however, give a slight reaction with the plasma of a donkey. The two species must, therefore, have very similar blood proteins, just as they have very similar body construction. This is just what one would expect if they are closely related by descent from a recent common ancestor, from which they have evolved.

The test for human blood, always coming up in detective fiction, is entirely similar. Rabbits are injected with known human blood and their serum tested against the unknown sample. If a clear precipitate forms, the suspected spot contained the proteins of human blood. Further, just as donkey blood gives a faint reaction with horse precipitins, so does ape blood give a slight reaction with human precipitins. Draw your own conclusions about a blood relationship between man and "monkey."

Immunity. You may have wondered why certain diseases never attack the same person twice. We say that a person who has once had diphtheria or scarlet fever or smallpox or typhoid fever or a host of other ills is "immune" to this or that disease, for it is most unlikely that it will be contracted again. The secret of this immunity lies in the antibodies (and to some extent in the cell mechanisms), for in such cases the specific antibodies which destroy the disease-producing organism continue to be present in the blood throughout life. Indeed, these antibodies, or immune bodies as they are also called, can be obtained from the blood of such immunized individuals.

The diphtheria bacillus, for example, remains in the throat but sends through the body a powerful protein toxin which produces heart failure and paralysis. The body, in turn, develops an immune substance which destroys the poison, an antitoxin, and, having learned the trick, continues to produce antitoxin in liberal amounts. By injecting horses, therefore, with diphtheria toxin, waiting for their blood to contain antitoxin, partially purifying this ready-made toxin destroyer, and inject-

ing it into children overwhelmed by an acute diphtheria, it is possible to destroy the poison and bring about almost miraculous cures. Or again, injection of killed typhoid bacilli into a man stimulates his body to produce its own typhoid antibodies and so renders him immune to a subsequent attack of typhoid fever. Vaccination against smallpox depends, in the same way, on activating the body to develop its own immune substances; but in this case, instead of killed smallpox virus, the closely related and practically harmless cowpox virus is used as the "vaccine."

Sometimes immune reactions "backfire" and, by a too sudden breakdown of foreign proteins, flood the body with their toxic fragments. Hay fever, hives, asthma, and like forms of allergy are mild examples of this; and the occasional sudden death when foreign serum is injected is an extreme one. These examples indicate the importance of immune phenomena; in fact, a whole new branch of medical science, immunology, is devoted to them.

Synthetic bactericides. It is a natural step, from the specific bactericidal antibodies produced by living organisms, to attempt to manufacture such chemical agents. Workers in this field of "chemotherapy" seek to make relatively simple substances able to destroy infecting organisms without injuring the body cells. The quest has been pretty blind and empirical, for we know so little about the composition of different protoplasm, and no antibodies have been made outside of living organisms. Nonetheless, several outstanding successes have been achieved and thousands of lives are being saved with synthetic drugs. You are familiar with 606, salvarsan, in the treatment of syphilis, with sulphanilamide in blood poisoning and other streptococcus infections, and with sulphapyridine in pneumonia. This last dread disease is being rapidly conquered by immune and chemotherapeutic treatments. Half a dozen Nobel prizes have been awarded for outstanding work in immunology and chemotherapy.

We cannot, however, go further into these fascinating subjects, but must attend to other aspects of autocatalysis or specific

synthesis or growth, foreshadowed in cell multiplication and in the synthesis of specific chemical defenders.

REPRODUCTION. Growth in most animals starts with the fertilized egg, or zygote, as the first cell of a new individual. We have seen something of the female reproductive system, especially the regular periods of growth and discharge of the

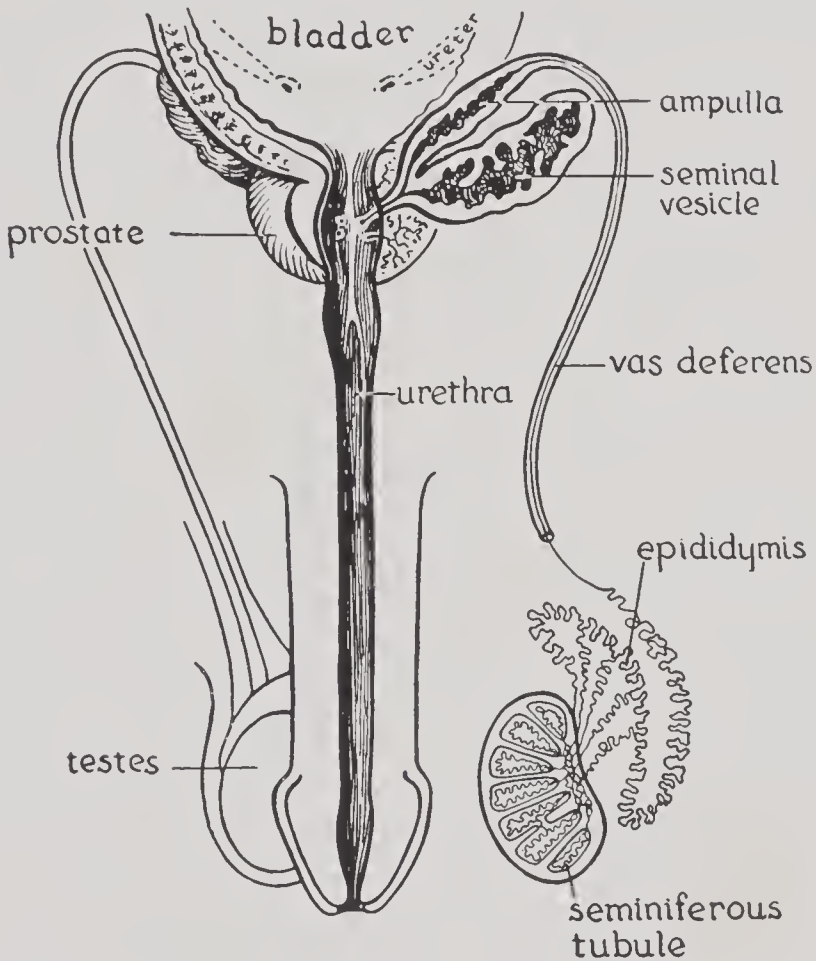


FIG. 79. The male reproductive system. (Drawn by E. M.)

egg and of growth and subsequent shrinkage of other reproductive organs—all controlled primarily through hormones. A reasonably similar situation obtains in the male. Special cells in the testes divide twice to produce four sperm each (spermatogenesis) continuously from adolescence to old age.

Spermatozoa. It is a curious quirk that sperm do not form when these cells are at the usual body temperature, but only when they are two or three degrees cooler. When, through

some abnormality in development, the testes fail to descend into the scrotum, sperm are not produced; but normally these organs are carried in this relatively thin skin pouch, and so remain at a lower temperature, and develop their living products. Whatever the explanation of this peculiar behavior, the ease of removing the testes has had a profound influence on animal husbandry and human affairs.

The newly formed sperm pass through fine collecting tubules, through the long coiled tube (epididymis) which caps one side of each testicle, and to the seminal vesicle, a sac which forms and stores a secretion that helps activate the spermatozoa. This vesicle is reflexly stimulated, by impulses from special touch receptors in the skin of the glans penis, to contract and discharge its contents. The suspension of sperm then passes the prostate gland and other lesser ones, which contribute to the white sticky fluid, semen, finally discharged through the urethra. By the time the male units are deposited in the vagina or uterus their long tails are actively whipping, they swim up the ovarian tubes (actually directed by the downward beat of the cilia of the tube), and one succeeds in fertilizing the ripe ovum, if present. The fertilized egg is slowly propelled by the cilia to the uterine cavity and there "eats its way" into the prepared thickened mucous membrane.

A good start in life. During the days required for this trip, the zygote has begun development by dividing progressively (into two, four, eight, and so on, cells) and forming in the main cell mass two cavities separated by a special plate of cells. This plate becomes the embryo proper while the more peripheral cells develop into the various membranes: the amnion, the thin fluid-filled sac in which the growing embryo later floats; and the chorion, which cooperates with the uterine mucosa to form the placenta, with which the embryo remains connected by the umbilical cord. The embryo's own blood flows through the umbilical vessels and the inner layer of the placenta; but it is always separated by capillary walls from the mother's blood, flowing in large blood sinuses on the outer surface of these same capillary membranes.

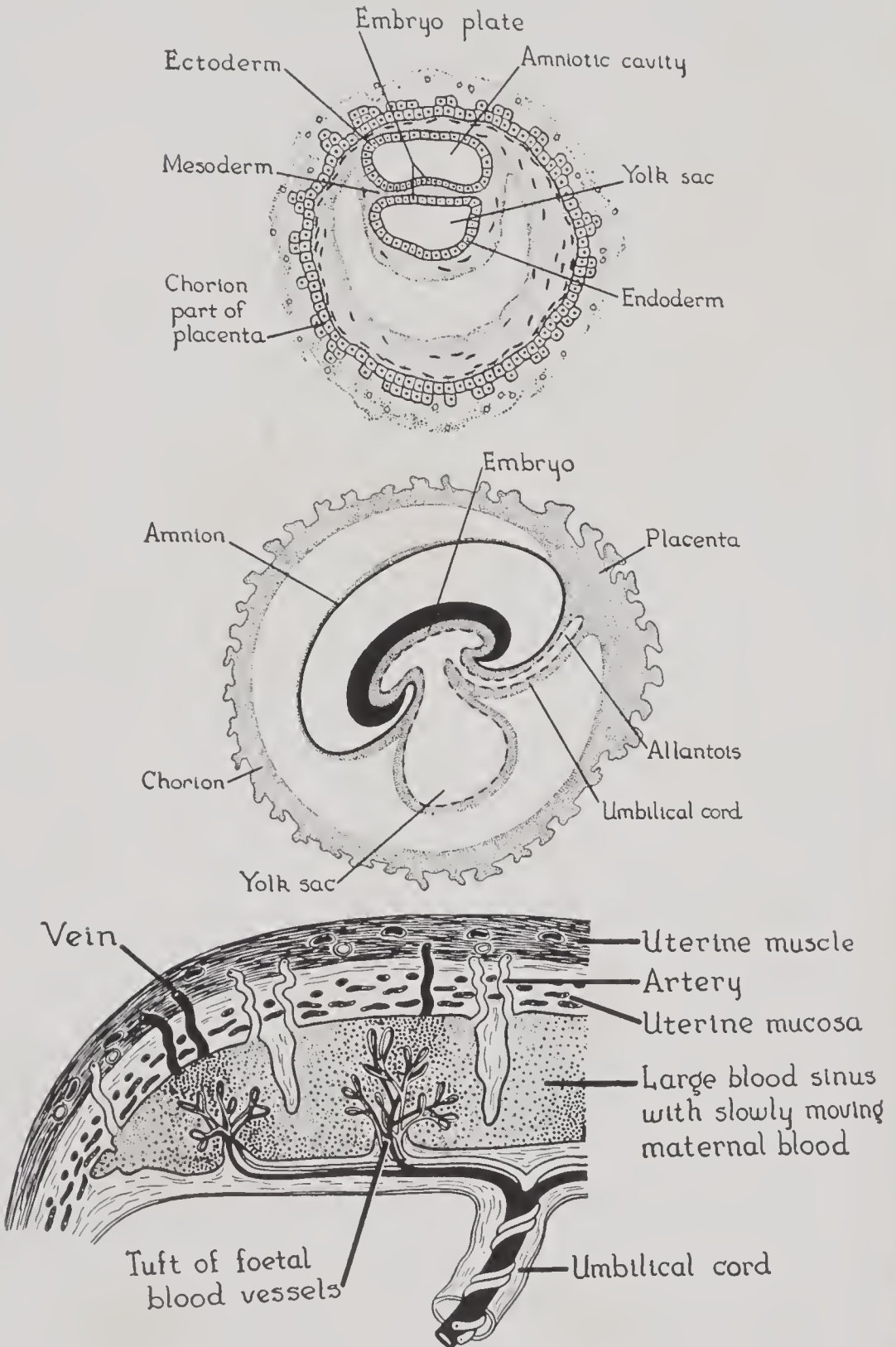


FIG. 80. These drawings show, from the top down, a very young embryo in the uterus; an older one with a developing placenta (solid black is ectoderm, stippled is mesoderm, and dotted is endoderm); and an enlargement of the placenta itself. In the placenta substances pass between the circulation of the embryo and that of the mother by diffusion across endothelium, without the two blood streams ever mixing. (Drawn by E. M.)

No nerves connect the embryo and its mother, and no mixture of blood occurs; but diffusion carries oxygen, sugar, amino acids, carbon dioxide, urea, etc., across the intervening endothelial cells just as between plasma and tissue fluids. The embryo is thus nourished and its wastes removed; and this "after birth" thus serves the young organism as lung, digestive tract, and kidney. Later, the fetus discharges some wastes into the amniotic fluid; but, of course, the fetus does not become physiologically independent until after birth. Even then a special food is prepared for it by the mother's mammary glands, developed for this duty during pregnancy, under the control of hormones. It is the possession of breasts, *mammæ*, by all mammals which gives the name to this class of vertebrates.

The whole sweep of evolution shows a progressive improvement in the devices used to give the young a good start in life and so to increase their chances of survival. Milk was the important "invention" by the first mammals, followed, in successive groups, by placental improvement which allowed the young to remain for ever longer periods in the protective uterus. This prolonged care of the young before, and particularly after, birth is most marked in man himself; and, aside from the favorable biological results, has had important social consequences. (Insects which form societies or colonies, as the ants, also nourish their young for a relatively long time.) Since mother and child, at least, must remain together for years, a closely knit family was the necessary consequence; and since, during these years, the infant is immature and so capable of modifiability and learning, there is opportunity to transmit social habits and achievements to a far greater degree than would otherwise be possible.

GROWTH. But what of the growing embryo itself? From indifferent materials, it is synthesizing its particular enzymes, proteins, and cell structures, and is increasing in mass and complexity.

Increase in size. If one cell forms two like itself, each of these two, and so on, the rate of growth should steadily ac-

celerate, and so it does. This period of augmenting growth, however, reaches a climax, at three to four months of embryonic life, after which the rate decreases and is zero when adult stature is reached. There is no break at birth in the growth curve, except for accidents of malnutrition; size increases smoothly, though ever more slowly, until adolescence. What turns the accelerating curve of the young embryo into the

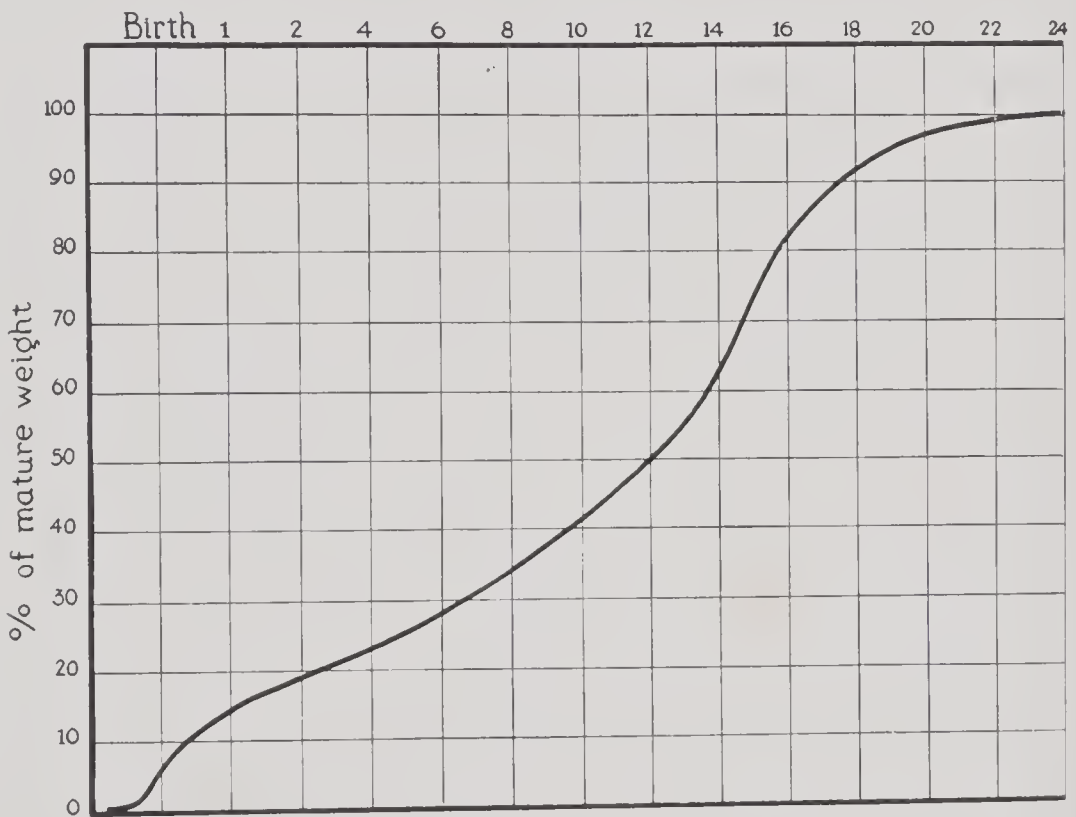


FIG. 81. This curve shows the increase in weight with advancing age (years shown above) for the average human individual, from conception to maturity. Note its S-shaped appearance in the early years and the renewed spurt of growth, which forms another S, at adolescence. (Drawn by E. M.)

diminishing one of later life we do not know; but it is surely an expression, beginning well before birth, of the phenomenon of aging. Perhaps the pituitary is somehow involved, for loss of this gland leads to senility in early life.

We cannot examine the causes of aging and ultimate death, but one peculiarity in the growth curve needs attention. You have surely noticed the sudden spurt of growth at adolescence. During two or three years, then, a boy may shoot upward

over a foot, mainly owing to growth in the long bones of the legs, making a sharp break in the previous smooth increase of height. Occasionally this increase is excessive and may start earlier, and giants standing eight and a half feet or better may result. Now what causes this sudden growth and why is it timed to parallel the sudden growth and maturation of the

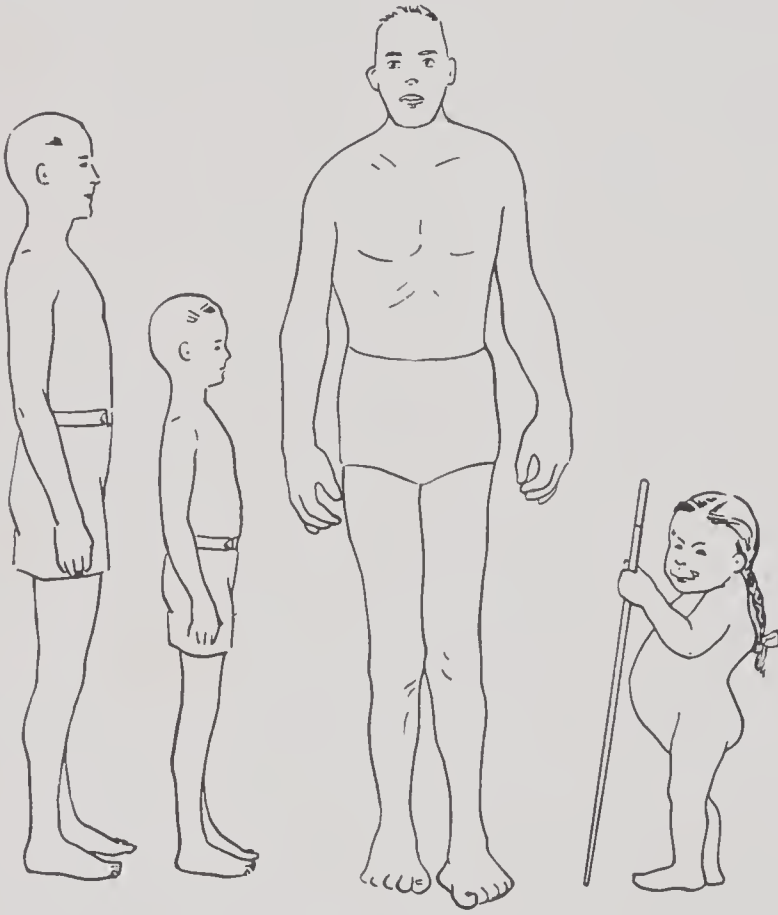


FIG. 82. These silhouette drawings illustrate the influence of some endocrine glands on body build and size. From left to right are shown a normal man, a twenty-one-year-old man with infantilism due to anterior pituitary defect, a giant resulting from excessive pituitary activity in childhood, and a ten-year-old cretin dwarf with congenital thyroid deficiency. (Drawn by E. M.)

sex glands? The control in the latter case we saw comes from the hypophysis, via gonad-stimulating hormones, when it reaches its own maturity. A similar pituitary hormone might be found to control bone growth.

A long story of fascinating scientific detective work proved this guess correct; yet another hormone from the anterior lobe of the pituitary is the guilty party. When this part of the

gland is removed from the young animal, growth remains stunted; when appropriate preparations of the gland are administered, overgrowth results; and when a tumor of the hypophysis occurs in a growing child, gigantism results. Other glands play a lesser role in controlling growth and development: the thymus, beneath the breast bone, and the pineal, sitting on the thalamus, perhaps contribute in the first few years of life; and the thyroid is also necessary for normal growth, for when it is removed in infancy (or, in man, fails to develop because of hereditary defects) a type of dwarfism results.

Increase in complexity. Growth in size, however, is but part of the picture; even more striking is growth in complexity. The zygote divides into two like cells. In many species, these can be artificially separated and each then becomes an entire normal individual; indeed, such a separation in the human being is the probable cause of identical twins. Yet sooner or later the cells formed by successive divisions are no longer alike; some turn into brain, some into muscle, some into liver, and so on. Even the first two cells, normally left together, become only a right and a left half of the body. Clearly, then, the fate of an individual cell depends partly on the circumstances in which it develops. If one cell may become a whole body or only a right half, perhaps later in development a cell could still become either bone or muscle, skin or nervous system, intestinal lining or liver. We have, in fact, already seen that, throughout life, many cells continuously change their structure or can do so under provocation—sperm and eggs, the various kinds of blood cells, skin and other epithelial cells, are continuously being produced from less differentiated ancestral cells; and white blood cells invade injured regions and become connective tissue.

Another great field of biological research has been the analysis of those factors which normally direct the differentiation of cells. Nervous influences play little role since the main organs of the developing embryo are well laid out before the nerves, growing out only from the fairly well-developed central nervous system, can reach them. The control must,

therefore, be through chemical agents and through such physical factors as position, pull, or pressure. Actually, all play a role, different in different cases.

For example, a hollow bubble of nerve cells grows from the newly formed brain towards the embryonic skin of the head to become later the retina. But the eye lens is formed from skin; and the two must be properly related. As the retinal cells approach the epithelium, this produces its own turned-in cell bubble, which becomes the lens. It is the presence of the developing retina which causes this skin action, for if it is cut away and placed, say, under the abdominal skin, no lens develops in the usual position on the head, while a perfectly good but useless one appears on the abdomen. In this case, chemicals from the nerve cells are the important agents. The development of striated muscle cells from a primitive connective tissue mass (mesenchyme or embryonic mesoderm), however, is more dependent on mechanical factors. The first chapter told how muscle structures line up in the direction of pull; similarly, a transplanted muscle, kept under tension, retains or develops typical striated fibers, but left unstretched it turns into connective tissue.

Hypertrophy. You thus see how vague is the line separating normal growth and development from repair processes, or from the changes induced by normal functioning. The same mechanisms control the original development of a bone and the repair of a broken bone. In both cases, general shape and deposition of calcium salts to give rigid support are determined largely by the weights to be supported; even the curved leg bones of a child with rickets will, when the disease is controlled and normal growth permitted, tend to straighten by developing more on the inside of the arc. The skin of a baby's sole is no thicker than that of its palm; but when walking begins this much-used surface becomes thick and tough by increased growth of the skin cells.

In fact, you are familiar with the general phenomenon that increased use or function of an organ leads to an increase in its size, hypertrophy. The bulging biceps of the blacksmith,



FIG. 83. These X-ray photographs of the shin bone show: on the left active rickets with considerable curvature of the bone and leg; and on the right a healed case. Note in the healed bone how the newly deposited bone layers (identifiable by the extra heavy white shadows) have been laid down largely so as to straighten the curvature resulting from rickets. (Courtesy Roentgenology Staff, Billings Hospital.)

the heavy calves of the ballet dancer, the enlarged heart of the basket-ball player, like the tough soles of the barefoot boy, are commonplaces. (See Fig. 72.) Less familiar, but equally important, hypertrophies occur in other visceral organs and, especially, in the various glands. In all cases, making an organ function at an intensity greater than normal leads to growth in size, and often in number, of the active cells.

Thus, when both adrenal glands are removed symptoms of adrenal deficiency sometimes appear for awhile and then vanish. It is found in such cases that small groups of adrenal cells, chancing to be away from the main glands and so left behind, have undergone marked growth and have developed into adequately functioning accessory adrenals. A bit of adrenal tissue less than one-fourth the normal amount can grow to full size. Similarly, when the thyroid gland is removed but little need be left, for this residue will develop and satisfy the body needs for thyroid hormone. In fact, a common form of goiter, or thyroid enlargement, is the result of such a functional hypertrophy. With an iodine-deficient diet the thyroid is unable properly to manufacture its iodine-containing hormone. Somehow, this failure stimulates the unsuccessful cells to even greater activity and finally to hypertrophy.

Controlling mechanisms. Now what mechanisms lead to hypertrophy; or to its opposite, atrophy; or, for that matter, to the normal growth of various organs and tissues? Some we have seen acting in the usual course of development, as the maturation of the hypophysis at puberty, although we have not identified the mechanism controlling this maturation. In other cases, the growth of one type of cell is determined by substances, usually hormones, produced elsewhere, as the gonads develop under the influence of hypophyseal hormones. Another striking case is the atrophy of the adrenal cortex, to one-tenth normal size, when pituitary removal eliminates a hormone continuously active on this gland.

These examples, however, do not cover the interesting regulation of cell growth by intrinsic activity, the functional hy-

pertrophies. At least two familiar types of regulation might be involved. One would be analogous to antibody formation and so a manifestation of autocatalysis. If the increased metabolism of active cells produced, besides waste products, substances which catalyzed the building of protoplasm, hypertrophy would automatically follow. The increased activity of phagocytes in digesting foreign proteins leads similarly to an increase in the cells' digestive enzymes.

But such an autocatalytic mechanism might run away unless some opposing mechanism automatically regulated it—recall our familiar example of high blood pressure initiating those reflexes which lower blood pressure. The thyroid hormone, for example, increases the respiration and activity of practically all cells. If it had the same effect on the cells of the thyroid itself, then activity and hypertrophy would necessarily accelerate to a catastrophic climax. If, however, while stimulating other cells, thyroxin acted to check those of the thyroid, activity would be automatically regulated. And this is exactly what happens; increased thyroxin inhibits the respiration of the thyroid gland.

The regulation of sugar by the liver is somewhat analogous. The rate at which liver glycogen is broken into glucose and discharged into the blood is partly determined by the actual concentration of glucose in the blood reaching the liver. When the blood glucose concentration is higher, the liver changes less of its glycogen, and vice versa. Or, again, orthosympathetic nerve discharges not only stimulate effectors but also liberate adrenalin, which further stimulates effectors. Since the adrenal medulla is itself one of the effectors stimulated, here is also the possibility of a blow-up. It has recently been shown, however, that adrenalin, though stimulating orthosympathetic effectors, tends to block nerve impulses at the synapses in sympathetic ganglia. Again an automatic check is set in action. As a final case, continued exposure to cold or chemical intoxication leads to a marked hypertrophy of the adrenal cortex. Since injection of cortical hormone prepara-

tions prevents this response, it would seem a clear case of supply and demand for adrenal hormone. Yet the pituitary is somehow involved, for no adrenal growth occurs if the hypophysis has been removed.

Cancer. Growth and reproduction are, of course, closely related; growth of a single individual depends on reproduction of its cells, and reproduction of a new individual on growth and division of particular cells, which separate from the parent instead of remaining part of it. We have seen how the elaborate body mechanisms which regulate its many activities can, rarely, break down and lead to disease. When those concerned with specific synthesis are involved, abnormal growth or faulty differentiation results. After long-continued overstimulation, for example, has produced repeated hypertrophy and many new cells, the overstrained mechanism goes awry. Chronic inflammation, leading to continued local production and destruction of new cells; repeated picking away a scab, so forcing the neighboring skin cells to grow and divide beyond any normal range; long-continued chemical irritation, from tobacco tar at the end of a pipe: these are some conditions that lead to such a final breakdown and cause the cells to grow and divide abnormally. The result is a cancer.

Cancer of the breast has been produced in mice simply by inducing repeated lactation while preventing normal milk drainage. Cancer of the stomach has resulted from infesting this organ with irritant parasites; and it regularly originates in man at the edge of a long-maintained stomach ulcer, digested away as often as it attempted to heal. Cancer of the skin is started by continued rubbing with coal tar and related substances, and occurs in men who handle these frequently, as chimney sweeps. (The particular chemicals identified as the active agents in these tars are very similar indeed to the male and female sex hormones.) Some types of chicken cancer are readily transmitted from one animal to another by injection of cell-free extracts of a cancer nodule, even in the absence of irritation. As with tar, special substances are responsible. And,

finally, cancer appears without any immediately discoverable cause, being determined largely by an hereditary predisposition; at least many strains of mice, produced by breeding, develop one particular kind of cancer in generation after generation.

It is not surprising to find many different "causes" of cancer, for this disease is one expression of a breakdown of normal growth mechanisms. Since growth itself is perhaps the most complex property of living cells, depending on the heredity with which the cell starts, controlled by all sorts of substances and forces acting upon the cell from without, and, finally, varying with the degree and conditions of the cell's own functioning and with the retroactive influence of substances produced by this functioning, we could well anticipate that one type of growth disturbance, cancer, might also result from hereditary factors, from special growth-stimulating substances, from excessive stimulation, and from growth itself, too long maintained.

The problem of cancer, despite the morbid fear which obsesses many people, is by no means insoluble. In terms of practical treatment and control, modern medicine is already very successful; surgery and radiation therapy can now completely free the great majority of cancer patients from the disease if treatment is begun in time. The difficulty with neglected cases is that the abnormal rapidly-growing cancer cells eventually spread widely into adjacent tissues, or they are carried by blood or lymph to lodge and grow in many far parts of the body. It then becomes impossible to remove or destroy the cancer cells without subjecting to the same fate the normal tissues of vital organs. But, though the practical solution of cancer is well advanced, and though our analysis of its nature is much greater than indicated by frequent pessimistic statements, it remains true that cancer will be really understood only when biologists have unraveled growth itself. Conversely, on the brighter side, almost everything we have learned about the basic nature of this disease brings us closer to an insight into one of the fundamental attributes of the life process itself.

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CHAPTER X

BEHAVIOR AND MIND

For simple organisms, as bacteria, or even tapeworms, there seems little "purpose" in existence other than that of successful reproduction. Few would take an identical stand about man or his cat, the insistent mosquito or the cold-eyed fish. All living things respond to feeble stimuli with a greater liberation of their own energy, directed adaptively to preserve their integrity. But this adaptive amplification, or behavior, seems to us of a different order in the "higher" animals than in the "lower"; indeed the position of an organism on this behavior scale is our main basis for the value judgment, "higher or lower." Clearly related to behavior is the central nervous system, especially the brain, the size and intricacy of which increases in parallel with the sensitivity, discrimination, variety, modifiability, and integration of behavior.

THE CENTRAL NERVOUS SYSTEM. Certainly in man we are likely to regard the continued fuss and fury of metabolism as pointed up for the nourishment and preservation, not of the reproductive system, but of the brain. There is considerable objective basis for such a view, for the central nervous system is surely the body's most cherished organ. Only the brain and spinal cord have a complete armor of skull and backbone. Within this rigid cavity, the nervous system floats lightly in its private bath of modified lymph, much as the precious embryo floats in the amniotic fluid in the womb. Three membranes, the meninges, also surround the very soft brain tissue and, being richly supplied with blood vessels, help carry into it its generous supply of nourishing blood. The circulation to the brain, we have seen, is especially guaranteed

by the carotid sinus which keeps constant the blood pressure at the brain portal. And finally, when, in starvation, the body must consume its own substance, the nervous system is yet preserved unchanged when muscle, intestines, etc., have faded to a vestige of themselves. A man fallen into poverty retains his possessions in the order in which he cherishes them; he

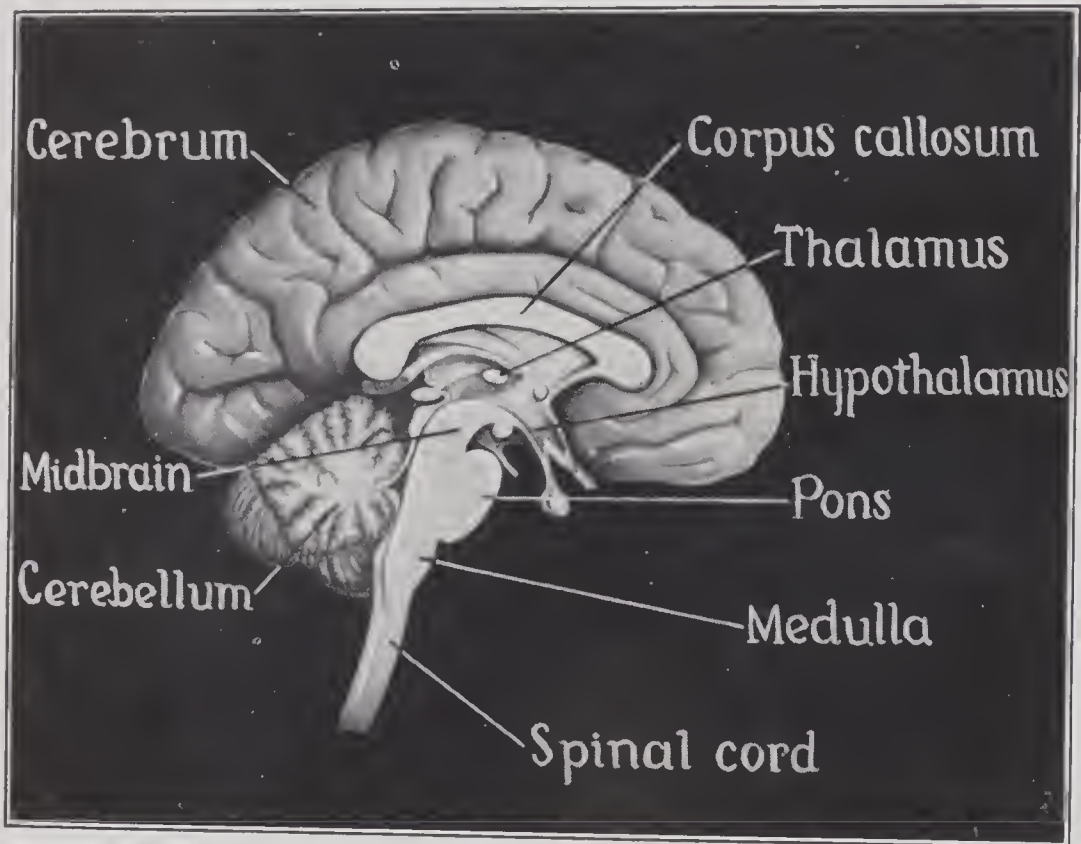


FIG. 84. This picture of the left half of the upper part of the spinal cord and the brain of man, cut in the mid-plane, shows the great cerebral hemisphere and the smaller cerebellum—the suprasegmental structures—as well as the various parts of the segmental brain-stem or neuraxis. (The corpus callosum is merely a great bundle of nerve fibers connecting the two cerebral hemispheres with each other.)

sells first what he values least. By this criterion our body indeed values its brain highly.

The brain stem and automatic behavior. It is time to be more precise about the central nervous system. The great length of it, running down the backbone and connected, by nerves emerging at regular intervals, to the bulk of the body, is, of course, the spinal cord. This extends upward into the lower part of the skull and widens laterally to form an oblong

“medulla.” Above the medulla, this “stem” of nervous system bulges into the “pons,” passes forward into the “midbrain,” with four domes on its dorsal surface, and still forward to the “thalamus.” Despite the very real differences in their detailed function, these portions of the nervous system can all be grouped under the terms: brain stem, neuraxis, or segmental nervous system. They are the modified descendants of the primitive ganglionated nerve cord, essentially alike down the body length, and composed of monotonously duplicated structures, such as the pair of nerves arising at each body segment.

True, in the vertebrates, extensive specialization of structure and function has developed in the brain stem; so much so that a neurologist can accurately locate, say, a pea-sized destruction by noting the unique symptoms it causes. Still, the whole neuraxis acts as an enormously complicated machine whose more-or-less repetitious behavior is thoroughly determined by its inborn structure. The brain stem, then, is that part of the nervous system responsible for automatic unlearned reflex behavior, is essentially alike from fish to man, and is the dominant part of the nervous system in all animals below the mammals.

The cerebral cortex and learned behavior. There are, however, other parts of the brain, the cerebrum and cerebellum, not present in the primitive segmental nervous system, but which have flowered from it in the course of evolution. These “suprasegmental” structures begin only at the reptilian stage of evolution to develop their highly special outer sheets of neurones, the cortex, which forms the gray layer surrounding, particularly, each cerebral hemisphere. This cortex is greatly increased in even the simpler mammals, is especially amplified in monkeys and other primates, and attains by far its fullest expression in man. The cerebral hemispheres occupy most of your skull, and half your quota of ten billion neurones is in its richly convoluted cortex.

The suprasegmental nervous system, especially the cerebral cortex, serves a basically different function than does the brain stem—although there is extensive overlapping—despite the fundamental similarity of the cells which compose both. These

are concerned with learned rather than unlearned behavior; they add the element of modifiability, perhaps even of choice and volition, to the automatic reflex action of the brain stem. If intelligence is defined as the ability to alter behavior in the light of experience—we commonly call one who fails to learn by experience a fool—then intelligence is almost uniquely an attribute of the suprasegmental nervous system. Further, as the functioning of the neuraxis depends mainly, though not exclusively, on its anatomically set pathways and connections, so the functioning of the cortex depends mainly, though not exclusively, on its changeable physiological state. Dynamic patterns of activity in its complex structure rather than static ones of structure itself permit individual modifiability or learning.

BRAIN AND MIND. Before examining further the different parts of the nervous system, you might like answers to some general questions about brain and mind. Where does consciousness come into the picture; do sensing and thinking surely depend on activity of the nervous system and, if so, how; is it true that a larger brain means greater intelligence; is there really a “free” will and what does the willing; and so on? I earlier admitted without reservation that we have no slightest explanation of *how* nerve-cell activity gives rise to the concomitant subjective experience of consciousness; but that it *does* I think can be proved.

Consciousness and neural activity. It is certainly not true that every nerve impulse or active neurone in the brain leads to a conscious awareness: the brain is not “dead” in deep sleep (electrical studies, to be mentioned, prove this); and when the spinal cord has been sectioned the lower portion still performs its reflex duties, yet the man so injured is aware of his lower body only as an external object. But it is true that there is no consciousness, such as we usually think of, without corresponding brain activity. Thus, in the man with the cut cord, sensory impulses prevented from reaching the upper nervous system produce no conscious sensation.

Destruction of the visual portion of the cortex leads to complete "psychic" blindness; yet the eyes continue to follow moving objects and wink when illuminated, and give the physical responses normally associated with seeing. Conversely, as we saw earlier, stimulation of one or another of the cortical sensory areas, by an electric current through the skull or a sharp blow, results in conscious sensation in the absence of actual light or sound. Similar stimulation by various drugs, shown to act on one or another brain region, results in the conscious awareness of non-existent things—the pink elephants and other hallucinations of the chronic alcoholic or of the hashish eater.

Destruction of relatively small parts of a cortical "association area," by a growing tumor or a sudden stroke leads to "aphasia." In aphasia, the ability to form concepts and give meaning, especially by the use of symbols—and all our language is based upon a use of symbols—is interfered with or abolished. The sufferer may, for example, be able to copy a written paragraph, proving that he sees, and yet be utterly unable to grasp its meaning. If you carefully copied a page of Egyptian hieroglyphics, it would still be "Greek" to you, but in the aphasic this is true for his own previously familiar language. Expert linguists, so afflicted, can write in English statements dictated in French and yet, when shown their own correct translation, make nothing of it but black scratches on a white background. The following marks . . . - - - . . . are just scratches to you unless you have learned the Morse code, but then they acquire meaning, "SOS," or "Help!"

In other forms of aphasia, from destruction of different association areas, the subject may understand written language but be unable to interpret speech; or he may have no difficulty in translating sensations into meaning, yet be unable to express his thoughts in writing, or in speech. If you have tried to get about a foreign country without knowing the language, you will have the idea. In still other cases, usually with larger lesions, the ability to form concepts through any avenue is impaired. The extreme is the amentia of the complete idiot—deprived of his precious cortex by some maldevelopment, or by

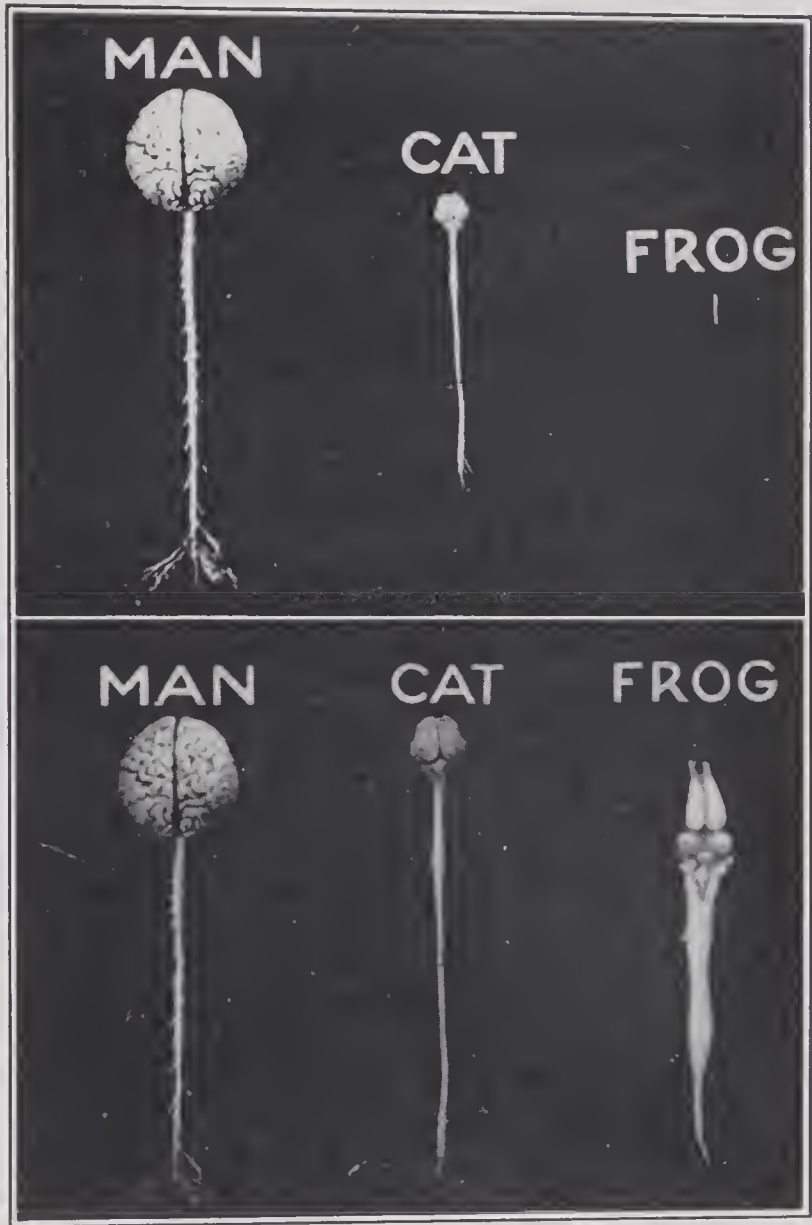
destructive brain hemorrhage at birth, or, most commonly, by an increase in pressure and amount of cerebrospinal fluid, causing hydrocephalus.

The insanities afford further evidence. General paresis was, a few short decades ago, a mysterious visitation of devils. Now it is known as one consequence of infection of the brain by the spirochete of syphilis; the actual neural destruction has been seen and correlated with symptoms; and there is even available an effective treatment, the production of high fever. Finally, consciousness can be completely suspended by all manner of agents which depress brain function; concussion from a sharp blow on the head; fainting and coma when the brain's oxygen supply is interfered with (by general circulatory disturbance or by high cerebrospinal fluid pressure collapsing the brain vessels); and, of course, the unconsciousness produced by hypnotics and anesthetics, which lower brain metabolism. There can be little doubt that our subjective awareness depends upon the nervous system and is predominantly (we shall see not exclusively) a function of the cerebral cortex.

Brain size and intelligence. We can glance at just one other question: Is intelligence dependent upon brain size? Naïveté can soon get us into difficulties here. Certain it is that, broadly over the evolutionary spectrum, mental capacity and cranial capacity increased together; and that, as the brain of any animal is progressively destroyed, its behavior deteriorates—again consider the idiot. In fact, rat experiments, depending on the ability to solve a complex maze as a measure of intelligence, showed that the amount of intelligence lost by an animal was accurately proportional to the mass of its cortex destroyed. On the other hand, dwarfs are not notoriously less intelligent than giants, nor small dog breeds than large ones. And the whale has a cerebrum many times larger than has man, yet men hunt whales and not the reverse.

This brings out the danger that lurks in a blunt question such as originally asked. You are probably ready with the reply, "Of course the whale has the larger cerebrum, but in proportion to his weight it is much smaller than man's." True

enough, but our question now becomes, "Does intelligence parallel brain size, expressed as a fraction of body weight?"



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FIG. 85. The entire central nervous systems of man, cat, and frog are shown, above, in their true proportions; and, below, when brought to equivalent size. Note that even when allowance is made for the different size of the animals, the cerebral hemispheres of the cat are relatively much larger than the carrot-shaped hemispheres of the frog and that those of man are far larger still. (From the film, *The Nervous System*, by Gerard.)

There are still difficulties, for a few birds and even some monkeys have a nervous system constituting more than two per cent of the body weight, the figure for man. Man's cere-

brum averages more in weight than woman's; but woman's cerebrum constitutes a greater percentage of her total body mass. To settle the argument, you need only decide which is more intelligent; but be prepared for trouble when you raise the question at the dinner table.

The real difficulty, of course, is that even so seemingly definite and measurable a thing as brain size is dependent on many subsidiary factors. How, then, can we even talk of the amount of intelligence before establishing criteria for measuring

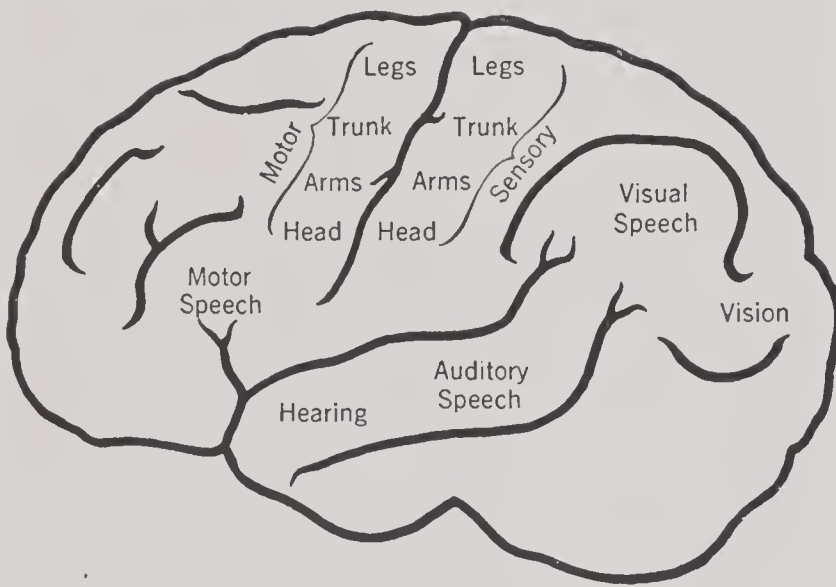


FIG. 86. This drawing of the lateral surface of the cerebral cortex of man shows the sensory and motor projection areas which directly connect with the lower parts of the nervous system. The three regions labeled "speech" are primary association areas related to the respective projection areas nearby. (Drawn by P. McC.)

it—to say nothing about some agreement as to its very nature? Consider brain size. If we call "brain" everything above the spinal cord we include much segmental as well as the supra-segmental portion. If it means only the cerebral hemispheres, half of these, even in man, are composed of mere fiber bundles (white matter) and deeper nuclei (gray matter) which are far more primitive than the cortex. Even the weight of cortex itself—which now offers difficulty in measurement—is far from a perfect criterion.

Projection and association areas. Those areas of the cortex which directly receive sensory impulses via "through" pathways

from one or another receptor—and the equivalent “motor” areas, axones from which run down the brain stem, set off

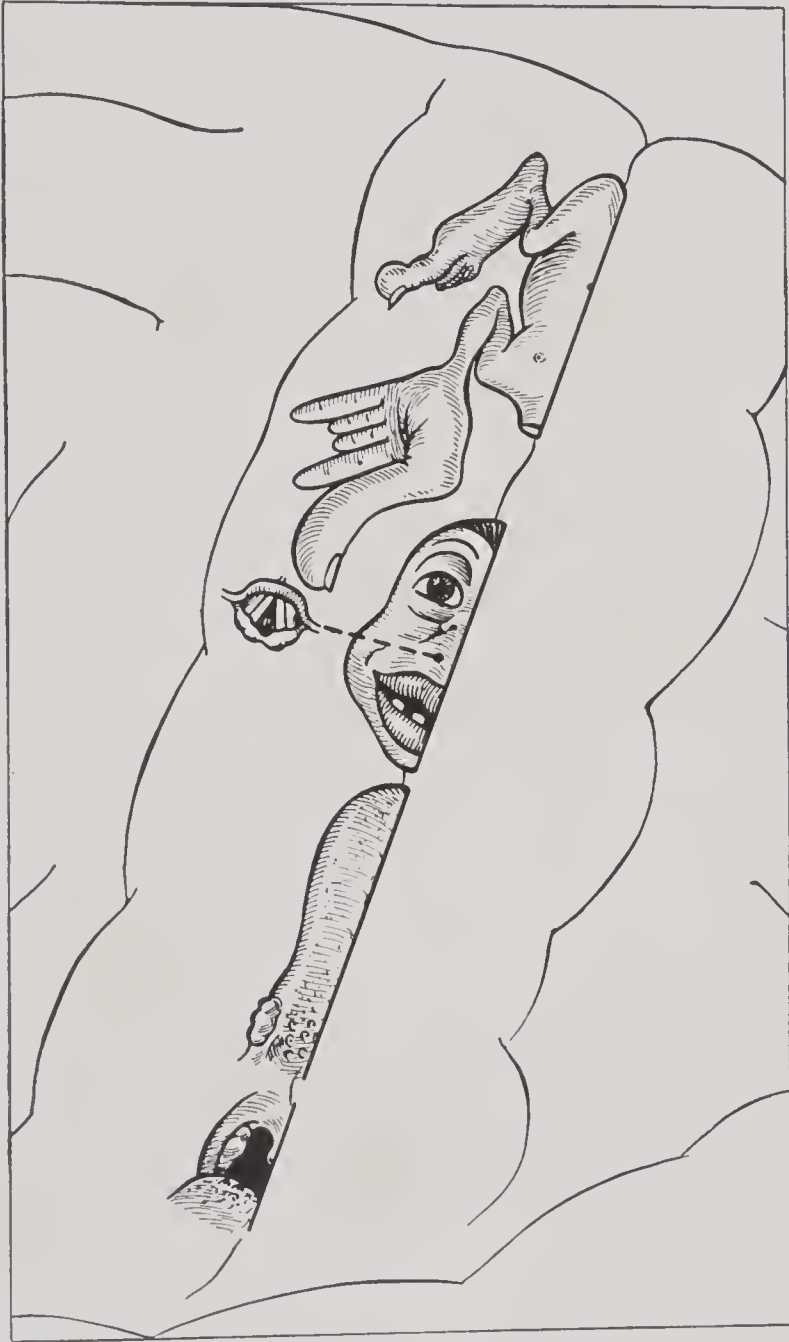


FIG. 87. The representation of body parts in the motor area of the cerebral cortex is not in proportion to the anatomical size of the part but rather to the delicacy and skill with which its movements can be controlled. This grotesque manikin, lying inverted on the brain surface, represents the approximate size and position of the cortical region for control of each of the body parts. Compare with preceding Fig. 86. (Modified from Penfield, drawn by E. M.)

spinal cells, and cause “voluntary” motion—must vary somewhat in size with the number of their peripheral connections.

Thus, an animal with large, finely discriminating eyes will have a larger optic cortex than one without; and an animal with many finely controlled muscles must have a larger motor cortex than one with a diminutive musculature or whose movements are few and crude. That part of the human motor cortex which controls leg movements, for example, is much larger than the equivalent cortex in the rat; although the rat is probably more skillful with his small hind legs than we are with our large ones. But the motor area which controls our arms, particularly our hands, and especially our thumbs, is disproportionately large for the part moved, the cortex area varying with delicacy and skill rather than with mass.

These various sensory and motor "projection areas" collectively occupy nearly all the rat's cortex, a good part of the dog's, a moderate amount of the monkey's, and but little of your own. The remaining cortex, which increases in size to its precipitous maximum in man, is not directly connected with any underlying portions of the nervous system, but serves for association between and integration of the projection areas which are so connected. Perhaps, then, the weight of these association areas, rather than that of the whole cortex or brain, would more closely parallel intelligence; for this, after all, surely involves the ability to see correlations, make associations, and perform integrated acts. This is close, but ultimately complexity and elegance of circuits and connections, rather than total mass, are responsible for superior performance—as a good small radio compares with a poor large one. The brain of Neanderthal man, the extinct inhabitant of European caves some 50,000 years ago, was actually larger than ours, although all anatomical and cultural evidence indicates that he was a more primitive human being. The fossil skulls show, however, that the occipital lobe, mainly visual projection area, composed an undue fraction of his brain. Perhaps he saw more keenly than we yet had smaller association areas and was less "intelligent."

Measuring intelligence. So much for brain weight; what then for imponderable intelligence? We can define and

measure this in the rat in terms of such a standard as the ability to learn a maze; and so long as this particular criterion is adhered to no difficulties will arise. But, even in the rat, when different tests are applied as a measure of intelligence, individual animals may score in a different order; and in man the situation is worse. If we were to test a thousand people for their ability to solve crossword puzzles, we could certainly

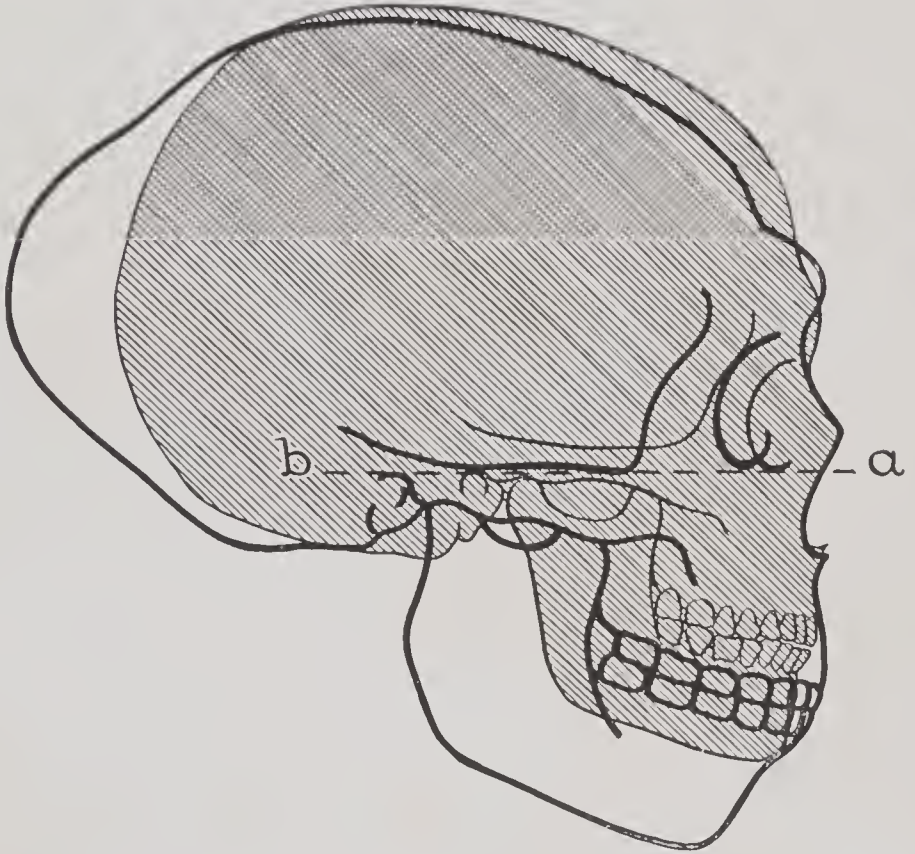


FIG. 88. These outlines of the skulls of modern man and his Neanderthal relative indicate the development of their respective brains. Neanderthal man, with the larger occipital lobe but smaller frontal one, could probably see better but not reason so well as ourselves. (Drawn by E. M.)

obtain a fairly consistent "intelligence" ranking. But if the same individuals were rated on their ability to solve chess problems, or to learn a foreign language, or to play a musical instrument, or to "win friends and influence people," or what you will, their relative "intelligence" ranking would probably be quite different for each type of test.

A pragmatic test of intelligence, making a "success" in the world, might leave us worse off, because so many personal and

social factors—opportunity, family connections, good nature, ambition—certain to be excluded from any definition of intelligence, influence the result. Yet most of us feel able to judge the intelligence of our acquaintances. And, indeed, the judgments about any one person by a number of others are sufficiently consistent to prove some validity, despite their uncertain basis. Psychologists faced the problem, then, of devising a set of strictly objective tests, permitting quantitative rating, applicable to the measurement of this somewhat nebulous intelligence, and yielding results consistent in themselves and in reasonable agreement with intuitive common-sense judgments.

You know something of the tests devised for intelligence, aptitude, attitude, achievement, and (in growing numbers) personality. Some, as performance tests, admittedly measure the results of using intelligence rather than the intelligence itself—the ordinary course examination attempts to determine what you have learned, not how easy or laborious was the learning. Intelligence tests, on the other hand, are intended to measure inborn ability and to be independent of schooling and general upbringing. This is admittedly a difficult, if not impossible, line to draw—for example, any test using language depends not only on innate capacity to learn a language but also on the child's social opportunity to pick it up—and there has been much argument and investigation of the extent to which "intelligence" tests do measure intelligence or measure schooling.

In these tests, the performance of "average" (already a problem) children at each age has been standardized on many individuals, and any particular child is then rated relative to the standard. When a child of six years chronological age successfully passes the tests normally accomplished by eight-year-olds, he is said to have a mental age of eight, and an intelligence quotient (I. Q.) of eight-sixths or, taking a quotient of unity as 100, an I. Q. of 133.

If the I. Q. measured only native intelligence, the figure for any one child should remain essentially constant through its development and independent of any social or educational

changes. On the whole this has been found to be so, though recent studies have reported changes in the I. Q.'s of children under changed environment—increases of as much as thirty points in the scores of previously underprivileged children placed in more satisfactory surroundings. Also, if the tests are for intelligence rather than experience, normal performance should increase with age, owing to mental growth, about as does body growth, and should remain unchanged once maturity is reached, although experience continues to pile up. Actually, test performance does improve rapidly in the early years, then more slowly, and at about sixteen a maximum is reached. According to present evidence, then, these tests do measure intelligence mainly, but not exclusively.

The aim in this early work was to obtain a sufficiently wide range of tests, so that the composite rating would agree with the common-sense judgments of teachers, friends, employers, and the like. This was achieved, for there is a high correlation of school grades, even of subsequent performance in a chosen field, with the I. Q. But from many viewpoints such a composite estimate is of little interest. The musical genius might be a business moron, or a brilliant philosopher be practically tone deaf, yet both score with the run of mankind on a battery of tests which averaged their talents. Perhaps, then, the general concept of intelligence could be split into its ingredients and specific tests devised for each. Psychologists are now making real progress in this direction.

At least eight mutually independent factors of intelligence have been already identified and each is being measured successfully by specific tests. Being independent, individual scores are sometimes very high on certain factors and very low on others. Some people test high in use of words and low with numbers, or are good at induction and pitiful at deduction, and so on. Of course the individual who performs poorly on many of these tests also shows a low I. Q. on the more general ones, and, similarly, the person possessing high talent in each factor manifests a high general intelligence; but, for the bulk of us,

such differential tests bring out individual strengths and weaknesses and are of especial use in making practical decisions. Indeed, when the particular qualities of intelligence (and of personality, likewise being split into elements and measured) required for successful performance in one or another vocation are known, such personal testing will be of great importance to the individual and community. Then, if we do not quite get round pegs in round holes, we shall at least get oval instead of square ones.

AUTOMATIC AND LEARNED BEHAVIOR. It is time to return from this most complex of human capacities to the nervous system itself.

Spinal reflexes. For contrast, look at the brain stem. The simple reflex is the prototype of all behavior. An impulse enters the nervous system along some particular afferent pathway, passes across synapses from neurone to neurone—in directions determined mainly by inborn structure—and finally emerges in motor nerves to produce muscular activity. Even this “simple” response, say the flexion reflex of the leg when a toe is hurt, we have seen to involve the elaborate and coordinated contraction of many muscles combined with relaxation of opposing ones.

The machinery necessary to this reflex; or to the knee jerk, which follows a tap on the tendon below the knee cap; or to the extension of, say, the left leg in response to the same stimulus which makes the right one flex; or even to the rhythmic scratching of the leg at an irritated bit of skin; all this machinery is located in the spinal cord, for these reflexes continue when it is severed from the upper nervous system. In fact, the hind legs of such a “spinal” animal may retain their normal posture (more often an exaggerated extensor posture) and the animal, once set upright, can stand or even walk, with the hind legs taking steps “on their own.”

This coordinated behavior depends heavily upon proprioceptive impulses from the muscles themselves, for when the dorsal

roots are cut and these sensory messages blocked, most coordination is lost. The knee jerk, for example, is a specific proprioceptive reflex; sensory impulses set up by stretching receptors in an extensor muscle cause just that muscle to contract. If the muscle is pulled and held, instead of briefly stretched, the reflex contraction is maintained as a continued tetanus. Since, in normal standing, gravity continuously tends to pull down our bodies, flex our legs, and so stretch our extensor muscles, this muscle stretch reflex is automatically called into play and the extensors are kept contracting just enough to maintain the posture.

The brain stem and posture. Overactivity of this stretch reflex, in fact, is responsible for the exaggerated extension of the legs in the spinal animal; and this suggests that other parts of the nervous system do influence spinal reflexes. When the spinal cord of man has been injured, but not entirely cut across, a similar "spastic" paralysis results. One leg, usually, can no longer be moved voluntarily, showing that one type of control from above is lost; yet it can give exaggerated reflex responses, including increased stretch reflex extension, showing the loss of another kind of control. Again, a local mechanism is controlled by opposing influences carried by nerves from other body parts.

Some nerve tracts descending in the spinal cord from higher regions act upon the motor cells to increase their reflex response, others act to inhibit. Actually, several successive levels exert such control, each higher region modulating the activity of those below. Thus, if the cord is cut across higher up, near its junction with the medulla, a control of the leg muscles by those in the neck can be demonstrated. When the head is bent forward the stretch in various neck muscles is altered, afferent impulses from some increase and from others decrease, the messages travel down appropriate paths in the cord, and the forelegs flex while the hind legs extend still further. If the head is tilted up a different pattern of stimuli is initiated, with the new result that the forelegs extend and the hind ones flex. But this, you see, is adding another fragment of normal behavior; when kitty lowers her head to lap milk her front

legs crouch and her hind ones stiffen, just as do those of the operated animal when the experimenter lowers its head.

When the brain stem is severed still higher, leaving the mid-brain intact, the ears remain connected, their balancing receptors help orient the head itself, and coordinated movements are perfectly normal. Here, then, is a cat which can roll on to its feet, get up, walk, run, climb, as well as a normal cat—with one big difference. It is a complete automaton, lacking all signs of intelligence. If, while walking, it gets caught in a chair it blindly continues the same movements, although a slight change in tactics could easily extricate it. It moves actively when hungry yet passes an open dish of food and, in fact, starves to death unless food is forced down its mouth.

Voluntary movements. The further contributions to movement made by cerebrum and cerebellum have to do with “voluntary” behavior—those even more complex and adaptive responses to the endless sequence of unique situations confronting the animal. Control originates in the motor area of the cerebral cortex, since injuries here prevent and stimulation brings about such movements. Careful stimulation of different parts of the motor area, of patients undergoing cranial operations, has shown that each part controls the movement of one portion of the body—a finger, ankle, eyelid, etc. But although these motions originate in the cerebrum, the cerebellum is necessary to their proper execution.

A person with normal cortex but with cerebellum damaged, by tumor or infection, makes his voluntary movements right enough, but so awkwardly. On attempting to pick up a glass, the arm moves forward irregularly, like a ship dodging a submarine, and, finally reaching it, the hand is likely to knock over the glass or the fingers to crush it when they grasp too vigorously. Compared to the smooth, swift, skillful movements you make, say in writing, those of a cerebellar patient resemble the blundering efforts of a child painfully guiding a pencil in its first words, with both hands, while tongue and eyes share in the inept movements.

The conditioned reflex. The cerebral cortex not only lends variability to behavior to meet the exigencies of the moment. It is also responsible, at least in their early stages, for slower and more permanent modifications of behavior. Such habits are a product of learning and depend on the particular experiences of the individual rather than on the evolutionary past of the race. The physiologist calls them "conditioned reflexes" and studies them quantitatively by measuring the response of the effector involved.

Salivary secretion, for example, is reflexly stimulated by food in the mouth. This inborn unconditioned reflex response is present in all normal individuals or even in the decerebrate animal. But the sight of real or even pictured food may also cause salivation. This response is not innate, nor alike in all individuals; it depends on "meaning" attached to the stimulus by the individual's past experience with similar stimuli. Thus, the odor of strong cheese, able to stimulate copious salivation in an Occidental, may produce in the Chinaman disgust, but certainly no saliva. A hungry dog, raised on a meat-free diet, secretes no saliva on seeing or smelling raw hamburger, although practically every normal dog would give a generous flow under these conditions. Further, after a few delightful experiences eating meat, the previously deprived animal comes to react normally. Removal of the cerebrum, in either case, abolishes this conditioned response.

The amount of saliva formed, then, serves to measure the development and control of such a conditioned reflex; and any other effector—such as the extensor muscle involved in the knee jerk—can serve as well. Results of such experiments show that almost any kind of stimulus, repeatedly administered along with some unconditioned stimulus, becomes a "conditioned" stimulus able to evoke the original unconditioned response. Food in the mouth is the unconditioned stimulus for salivation; when a bell is rung each time food is given, the conditioned stimulus of the bell finally causes salivary secretion when given alone.

You knew this from your own experience; the dinner bell often suffices to initiate your secretory preparedness for digestion. And you have certainly had the annoyance of inadvertently starting a set of automatic habitual responses—each step being stimulated by the preceding response and in turn initiating the following one—as when you start to change your shirt for dinner and suddenly discover that you have completely undressed. But precisely applied stimuli and measured

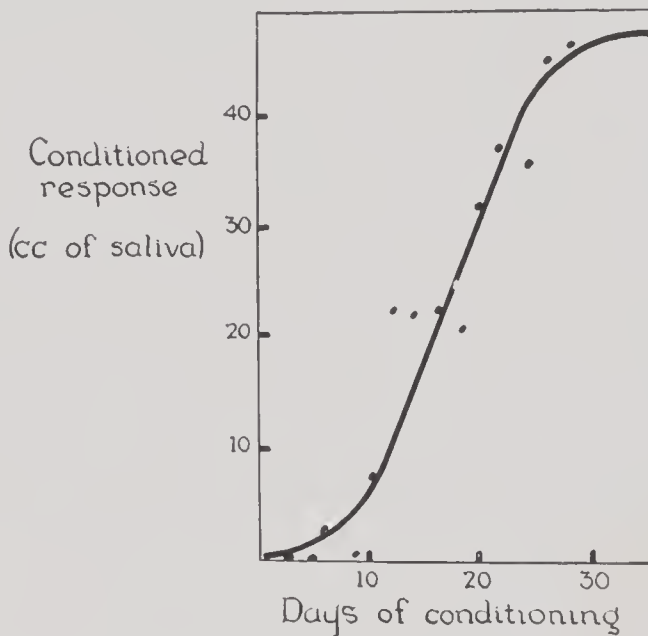


FIG. 89. This curve, showing the establishment of a conditioned reflex of salivation with repeated trials, is the typical S-shaped curve of learning, of growth, and of autocatalysis in general. (After Kleitman, drawn by E. M.)

responses have led to far greater knowledge than has our casual experience.

For one thing, the rate at which a conditioned reflex is established, with regularly repeated “training” periods, commonly follows a curve similar to that of weight during growth or to that of learning. The speed and accuracy with which a beginner performs, say, on a typewriter increase slowly at first and then more rapidly, but finally improvement slows down until his maximal performance is reached, when he has “learned” to typewrite. The number of drops of saliva secreted in response to a bell, rung just before each feeding, increases

along a similar course. Both are, in fact, learning phenomena; both depend on the cerebrum; both are individually acquired capacities; each can serve, in terms of the number of repetitions needed for a given degree of achievement, as a type of intelligence test; both record the learning process; and both are, perhaps, fundamentally related to growth—for learning is certainly, in several senses, a form of growth. (The sudden insight, when an idea “clicks,” is a different type of improvement and depends rather on establishing new relations between existing things.)

What neural mechanisms retain a residue of experience, what makes memory possible and able to modify current responses we do not know. I shall mention one very minor possible factor to emphasize the relation to growth. If adult neurones can develop new dendrites—and neurones of older brains are more branched—then new synapses can be established, new nervous pathways opened up, and new behavior patterns acquired. But how would such a simple explanation account for forgetting? The physiological theories are also far from satisfactory.

BRAIN WAVES AND DYNAMIC PATTERNS. A good beginning, however, has been made; and results of electrical studies of the brain promise greater insight. The old picture—of intricate pathways throughout the nervous system, lying inactive except as impulses from receptors sweep through—has been proved inadequate. It is not incorrect but woefully incomplete. An oscillograph or loud-speaker, connected through amplifiers to wires placed against your forehead and occiput, would record a continuous electrical activity of your brain. While you sit relaxed, thinking of nothing in particular and with eyes comfortably closed, your cerebrum is beating along steadily, producing about ten electrical waves a second.

These waves are so feeble that only after being magnified millions of times can they be recorded with our most sensitive

apparatus, so their discovery lends no support to the possibility of such phenomena as mental telepathy. But their presence in the relaxed person does prove that brain cells are continuously and spontaneously active and do *not* remain inert unless stimulated from elsewhere. This is particularly clear in the completely isolated frog brain or a bit of it, which continues

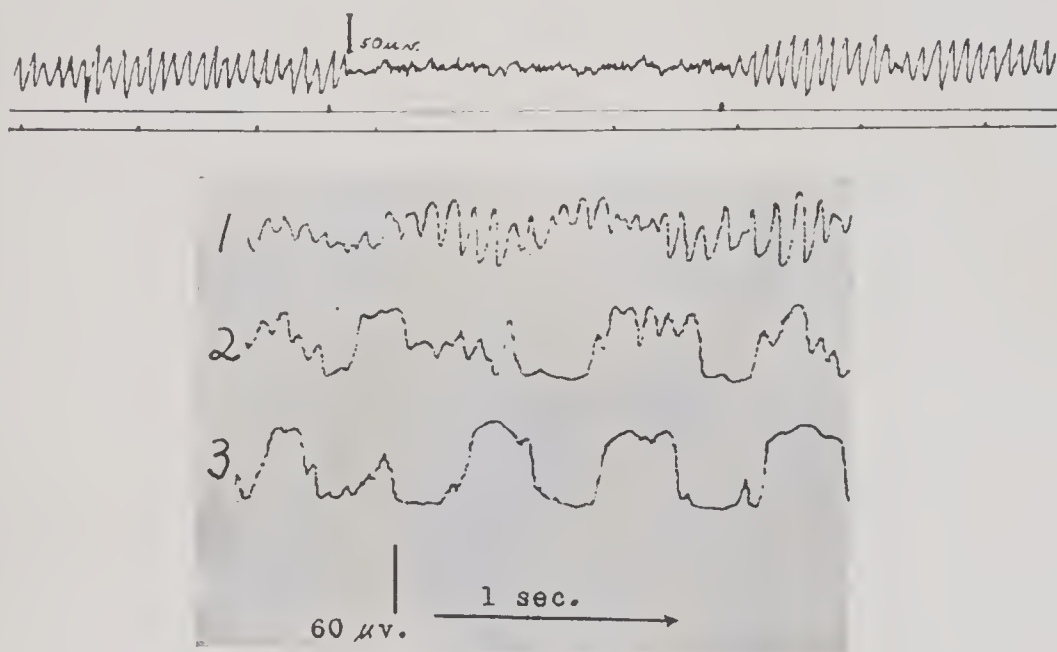


FIG. 90. These are records of electrical waves produced by the normal human brain. The upper one shows the characteristic rhythm, at about 10 a second, present in normal individuals while sitting relaxed with eyes shut. The lower horizontal line indicates seconds, the short vertical line gives the height on the record produced by a potential of one fifty-millionth of a volt. When the eyes are opened (during the interval between the two marks on the upper horizontal line) the brain waves disappear, to promptly return when the eyes are again shut. The lower record shows these same waves taken at a faster speed in the upper trace. The other traces (from above down) show how the brain waves become slower and larger as a person falls into progressively deeper sleep.

to generate regular electrical waves for hours. The brain waves, then, are our most direct index to the activity of the brain itself; they have already proved extremely useful.

Brain diseases change the brain waves; brain tumors can be located by noting where on the head abnormal waves appear, and epilepsy can be diagnosed by a particular kind of abnormal wave. In sleep also the electrical waves change, being much slower in deep sleep and varying characteristically with

sleep depth; it is possible to tell by the records from a sleeping person how loud a noise will be required to wake him.* The brain waves even give some information about the presence of dreams. And, in case you are wondering, the waves under hypnosis are not at all like those of sleep.

The important thing, however, is that cerebral neurones, and many others, are continually beating; indeed, great numbers are beating together, like a violin section of an orchestra. An incoming stimulus, then, does not simply travel a fixed path but rather changes one set of related actions into a different one, as if a kaleidoscope had been disturbed. Electrical ripples travel about the cortex, meet, interfere, and reinforce one another, and one dynamic pattern of activity shifts into another and yet another through the course of living and learning.

* Sleep is especially interesting as the only normal condition which markedly changes the brain waves; and it is also, of course, the only slow regular rhythm shown by the nervous system. In sleep the viscera continue their routine kitchen work with little change—although a slight slowing of heart rate, fall of blood pressure, and the like, indicate that the orthosympathetic system is somewhat less active—but the central nervous system, and of course the skeletal musculature which it controls, becomes much less active.

The basic rhythm of sleep and wakefulness seems to be determined by "centers" in the hypothalamus, for stimulation or injury in appropriate parts of this brain region can suddenly put an animal to sleep or produce continued somnolence. Disease of the human hypothalamus produces all sorts of sleep irregularities, including the ailment, narcolepsy, in which the sufferer falls into a "fit" of true sleep when emotionally excited. This basic rhythm, however, does not have a twenty-four-hour period; wake and sleep alternate at intervals of three or four hours only, as in babies and other young animals. It is only as the cerebral cortex assumes more control, and indeed develops a type of conditioned reflex to the presence or absence of general stimulation by day or night (differences in light, temperature, sounds, etc.), that the adult type of sleep cycle develops. The importance of the cerebrum in this is shown by the effects of removing it in the adult dog, for such an animal promptly reverts to the shorter period sleep rhythm of infancy.

Why any sort of sleep should be necessary is an unanswered question. One interesting suggestion, however, is that sleep is the normal state of existence and that being awake is a sort of emergency state brought about temporarily by the vital needs of hunger, cold, and the like. With the development of the cortex in the more advanced animals this inborn wakefulness of "necessity" is supplemented by the conditioned wakefulness of "choice."

THE THALAMUS AND EMOTION. So much for a hasty survey of the things we and our brains do. What of the thoughts and feelings which accompany behavior? Feeling is different from thought. It does not have to be learned, for the new-born baby gives every evidence of feeling pain or hunger; it is universally present, at least in the more evolved animals; it is alike in mice and men, for all normal individuals show similar manifestations of anger or fear or pain; it is accompanied by characteristic bodily changes, for you can conceal thoughts but not strong feelings; and it is constant and automatic, as an unconditioned reflex, rather than changing and subject to rational argument. Is it possible, then, that feelings or emotions are dependent on a part of the nervous system other than the cortex which makes thought possible?

Autonomic reactions. The bodily changes which accompany feeling—the dilated eyes, erect hair, clammy skin, and rapid heart of fear; the flushed face, pounding pulse, and widened eyes of anger; and so on—are all expressions of activity of the autonomic nervous system. We earlier saw how orthosympathetic discharges, controlled from a center in the hypothalamus, help prepare an animal to meet an emergency; might not this same brain part be concerned with the emotion which accompanies the awareness of that emergency? It is, perhaps, impossible to prove that feeling consciousness, or affect, actually occurs in the thalamus or hypothalamus, but it is simple to show that activity of this region is necessary to awareness and expression of emotion. Human beings with disease of the hypothalamus show marked emotional upsets, but the clearest evidence comes from animal experiments.

Affect. A cat with its nervous system intact up to the thalamus executes perfectly coordinated movements, but automatically. With the cut a few millimeters higher, leaving the hypothalamus connected to the brain stem, behavior is strikingly different. As such a thalamic animal comes from under the anesthetic it struggles violently against its ties and, when released, assumes an alert posture. A light touch, even stroking its fur, sets off a vicious attack. The cat hisses, bites,

strikes with its claws, arches its back, and thrashes its tail, at the same time that its pupils enlarge, its heart rate and blood pressure rise, and its hair bristles—in other words, it looks and acts exactly like an enraged cat confronting a barking dog. Or, an appropriate hissing or whistling sound causes the thalamic animal to give every physical evidence of fear—blind running with head and tail lowered, pitiful meowing, etc.

To avoid commitment as to whether or not these animals have an actual feeling awareness, they are said to be in a “pseudo-affective” state and to show “sham rage.” This precaution is wise. A large injection of adrenalin into a man produces all the autonomic manifestations of fear but the subjective report is, “I have the sensations of being frightened yet feel no actual fear.” Note, moreover, another point: just as spinal reflexes are increased when the cord is disconnected from upper parts of the nervous system, so the reflex expression of emotion is released when the cerebrum is removed. The thalamic cat is hyperemotional and gives exaggerated reactions to stimuli which are ineffective or soothing to the normal animal. Stimuli from the cerebrum can, of course, also discharge thalamic activity; else certain sounds, given meaning as “fighting words” only by your cerebrum, could not evoke conditioned affective reflexes. But the cerebrum’s predominant role here is to hold in check the reflex behavior discharged from the thalamus.

Insanity and neurosis. Various upsets of this balance can occur and the major insanities seem to involve emotional more than intellectual disturbances. In dementia precox, for example, memory and reasoning power may be unimpaired; and the patient who has stood in one position, dumb and absolutely unresponsive for hours or days, may later tell quite rationally all that happened during this episode of withdrawal. He remained fixed, he then says, because he felt a compelling emotional urge to do so. When the compulsion is to kill a person whom the patient hates, or more often fears, the consequences may be disastrous. Several treatments of this insanity are now producing encouraging results; but whether by im-

proving a defective cortical functioning or by correcting an exaggerated thalamic activity or in still another manner has yet to be proved.

Over- or underactivity of portions of the autonomic nervous system, perhaps induced via the thalamus by disturbed emotional states and exaggerated conflicts, leads to the "organ neuroses." A hungry man is proverbially ill-natured and, conversely, worry ruins the digestion. Carried further and kept up continuously, excessive activity of the vagus might produce too much stomach motility and too copious a secretion of acid gastric juice, and so lead to a chronic stomach ulcer. At least, physicians now recognize that ulcer treatment by alkali is often less effective than by relaxation of strenuous effort or by resolution, under psychiatric care, of emotional conflicts. There is even evidence that each kind of organ neurosis results from a particular type of conflict; and one branch of psychiatry, psychoanalysis, is studying intensively the conflicts which produce the unsatisfactory emotional states and behavior habits known as neuroses. Neuroses have, in fact, been induced in animals by presenting conflicts during conditioned reflex training. When, for example, one tone is used as a conditioned stimulus for "feeding" and another for "no feeding," all goes well until the notes are made so similar that the animal can no longer discriminate between them. It then becomes bad-natured, fearful, snaps and whines and mixes up its well-established responses, and even loses weight. Hamlet, likewise, burdened by conflicts beyond his emotional resilience, suffered a "nervous breakdown."

Emotion versus intelligence. Actually, however much our behavior may be directed by intelligence and rationally justified, the main drive to action (too often even the direction of action) originates in the emotions. Recall the behavior of a person after drinking enough alcohol to be chemically decerebrated—for this drug, like ether, depresses the cerebral cortex before it disturbs other parts of the nervous system—as an indication of the power and importance of the emotions. The psychoanalyst speaks of an "id," a primitive, selfish,

bestial part of the psyche, held in check by, and continuously in conflict with, the "super ego," the "conscience" developed by social precept and teaching. The physiologist sees the old top of the brain stem, the hypothalamus, initiating essentially the same unreasoned behavior throughout the whole gamut of vertebrates, but inhibited ever more by the evolving cerebral cortex. Feeling preceded thought. Descartes would have been more nearly right in saying, "I feel, therefore I am," than, "I think, therefore I am."

The control, however, is still very imperfect. Every experienced speaker, every successful politician or salesman, knows that an appeal to reason may develop conviction and understanding, but that the appeal to emotion engenders action and gets results. A painful stimulus causes the flexion reflex to break through the reflexes maintaining posture and balance; a throbbing tooth keeps one's attention from a symphony; and a strong emotion snatches from intelligence the reins of behavior and drives us headlong into deeds which our "better judgment" would sternly veto. You decide to marry a girl with a good heredity but find, when the time comes, that deep brown eyes determine the decision.

The primitive thalamus, the "selfish" brain, when stimulated to activity, always takes control away from the newly evolved, rational, educable, socialized cerebrum. It is man's modern cerebrum which enables him to entertain such abstract notions as justice, charity, goodness, and beauty; and it is his ancient thalamus which says, "Might is right and the devil take the hindmost"—and mostly gets away with it. If this seems dismal, be solaced by a light brightening on the horizon.

The cerebrum is educable and, by education, its function is developed and the conditioned reflexes which it controls are multiplied and strengthened. The knowledge and wisdom of mankind is cumulative and increasing. The emotions felt by the Athenians for their friends or city have not the slightest influence on those we feel today; but their art and philosophy and science formed pillars upon which have been reared our own esthetic and intellectual cathedrals. As Newton said, "If

I saw farther, t'was because I stood on the shoulders of Titans." The intellectual stores of civilization are increasing and with their aid a more effective functioning of the malleable cerebral cortexes of future generations can be achieved. I shall close, then, by echoing the words of a monumental volume on the nervous system by C. S. Sherrington, one of the great physiologists of all time: "It is then around the cerebrum, its physiological attributes, that the main interest of biology"—and, one might add, of psychology and sociology—"must ultimately turn."

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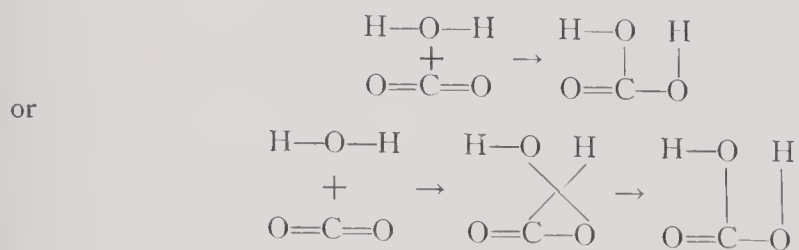
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APPENDIX A

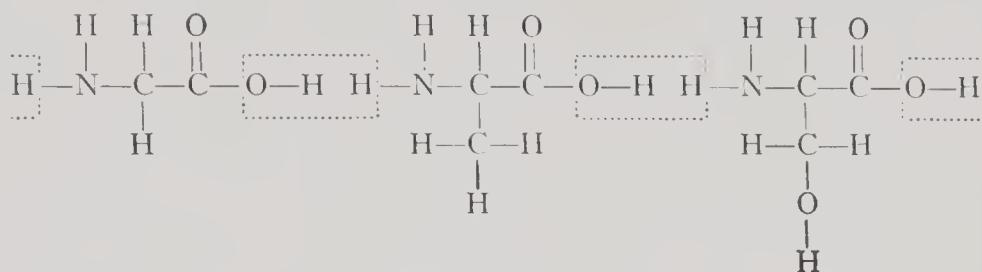
PROTEINS

Each kind of pure substance is composed of like molecules which are unique to it. The molecules of different substances differ from one another in the kind, number, or arrangement of the atoms which compose them. By using a symbol for each kind of atom (as O for oxygen, H for hydrogen, N for nitrogen, C for carbon, Cl for chlorine, Na for sodium—technically called natrium) and a line indicating the connection of one to another, we can draw conceptual pictures of molecules which help us enormously in understanding how they act.

A molecule of water, H_2O , has two atoms of hydrogen and one of oxygen, as this formula states, and would be pictured as H—O—H . A molecule of carbon dioxide, CO_2 , is practically described by its name and has the structure $\text{O}=\text{C}=\text{O}$. The two lines between each oxygen and the carbon indicate that the atoms in this compound are held together by two bonds. If one of them were to open and combine with other atoms, the oxygen and carbon would still remain attached. Thus it is possible for a molecule of carbon dioxide to add a molecule of water and form a new molecule, of carbonic acid. The chemist will show this either as the simple equation, $\text{H}_2\text{O} + \text{CO}_2 \rightarrow \text{H}_2\text{CO}_3$, or as structural pictures,



A protein molecule is built of many, usually hundreds, of amino-acid molecules which have become combined. There are over two dozen different amino acids, but their different molecules are all alike at one end where they combine with each other. Three of the simplest amino acids are shown in the following pictures, and they combine together with the loss of water molecules as shown. Each end of the resulting compound can continue to combine with new amino acids in the same way, and when enough have been hooked together the product is a protein molecule.



You will note that two of the substances already mentioned are called acids. To understand why, we must consider a very different property of certain kinds of molecules. The bonds which hold atoms together in a molecule are electrical attractions, the atoms at each end of a bond being of opposite charge and sticking together like opposite poles of two magnets. Water has the ability to decrease these attractions; with the result that certain atoms in the right kinds of molecules actually come apart when these are dissolved in water. In ordinary table salt, $\text{Na}-\text{Cl}$, for example, the sodium atom is the positive end of the bond and the chlorine atom the negative end. When dissolved, the two atoms completely separate, giving a positively charged sodium fragment, Na^+ , and a negatively charged chlorine fragment, Cl^- . Such electrically charged molecule fragments are called ions; in this case the sodium ion and the chloride ion.

Carbonic acid in solution similarly ionizes into a hydrogen ion and a bicarbonate ion, $\text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-$. Amino acids likewise split off a hydrogen ion from the rest of the molecule; and in fact any substance which gives hydrogen ions is an acid. Some of these ionize easily so that all the molecules are split and much hydrogen ion is produced. These are the strong acids. Others ionize only slightly, giving little hydrogen ion, and are correspondingly weak acids. Water itself ionizes to a minute extent, one molecule in ten million, into $\text{H}^+ + \text{OH}^-$ and is therefore an extremely weak acid.

Hydrogen ions and hydroxyl ions (OH^-) cannot exist together in the same solution, except in negligible quantities, for they promptly combine with each other to form whole water molecules. An acid can therefore be rendered inactive, or be neutralized, by adding to it any substance which yields hydroxyl ions. Such substances are known as bases or alkalies, and ordinary lye is a good example. Thus hydrochloric acid, HCl , plus sodium hydroxide, NaOH (lye), neutralize each other when mixed, to form water and salt ($\text{HCl} + \text{NaOH} \rightarrow \text{H}_2\text{O} + \text{NaCl}$). When any acid and base react, the products are water and a salt, of which sodium chloride is only one familiar example. Actually, until the water is removed, the salt is not present as such but as its two ions—the one contributed by the acid the other by the alkali.

APPENDIX B

COLLOIDS

Ordinarily when a solid is added to water it either dissolves or does not. In the latter case the individual solid particles, like sand grains, will settle to the bottom after any amount of shaking. Each such particle is composed of billions of molecules and is simply too large to remain suspended among the water molecules. When the solid dissolves, on the other hand, its molecules do not remain in clumps but separate from one another to become scattered individually in true solution, among the water molecules.

In certain cases, however, the added solid shaken with water separates, not into individual molecules but into very small aggregates of them. In other cases, as the proteins, the individual molecules of the solid are themselves so enormous compared to a water molecule that even a single one acts like such a small clump. In these cases the resulting liquid has properties somewhere between those of a true solution and a temporary suspension; the particles do not settle out but the liquid remains opalescent. Such an intermediate state between suspension and solution is known as a colloidal suspension or colloidal solution or simply as a colloid; and the tiny solid particles are known as colloidal particles. (Sometimes, when they are on the large side and elongated into rodlets, they are called micelles.)

Gelatin "dissolved" in water is a typical colloid and illustrates further another important property of these. When it is warm—that is, when the colloidal particles are moving about rapidly and remain separated from each other—the whole mass flows freely, as any ordinary liquid or solution. The colloid is then in the sol state. When cooled, which allows the now less active particles to stick together, the mass sets into a soft solid or jelly. The colloid is then in the gel state. Such a shift to and fro between fluid sol and solid gel is characteristic of most of the protein or fatty colloids which exist in protoplasm; but instead of depending on marked temperature changes such shifts are brought about by variations in the ions present or by other conditions which can be produced by the ordinary metabolic and other activities of living cells.

APPENDIX C

OSMOTIC PRESSURE

Individual bits of matter—ions, molecules, or colloidal particles—are forever in motion. Each moves straight in some direction until it collides with another bit and bounces off along a new path. In a solution both the water molecules and the dissolved units are thus continuously

jostling each other, and any one bounces its way very slowly from one place to another over the whole bulk of the liquid. If a lump of sugar is dropped into a cup of water, sugar molecules soon form a "cloud" around the lump as it dissolves. But now, of course, the "concentration" of sugar is high in one region of the water, near the solid lump, and low in other regions. The random movement of sugar molecules will bring a drift from the region of high concentration to that of low, since more molecules will inevitably wander away from a region of closer packing than will wander into it. This movement of dissolved particles through a solution, in a direction tending to equalize their concentration everywhere, is known as diffusion.

But, of course, that part of a solution containing more dissolved molecules in a given volume will contain fewer water molecules in the same volume, because the dissolved ones take up some of the space. Just as the dissolved units migrate from a region where they are crowded to one of less crowding so also do the water molecules; but when these move from a region with more water into one with less they are also moving from a region with less dissolved substance into one with more. Since the concentration of a solution is always expressed in terms of the amount of dissolved material, we say the water moves from a region of lower concentration to one of higher, in contrast to the solid bits which diffuse from a region of higher concentration to one of lower. This movement of the water molecules into the concentrated solution is known as osmosis.

Ordinarily both these processes occur without ado in any incompletely stirred solution. If two sugar solutions, one concentrated and one dilute, are placed in the same container but separated by a membrane which is permeable to both sugar and water molecules, again both osmosis and diffusion proceed automatically. If the membrane separating the solutions is impermeable to both kinds of molecules, nothing happens—any more than if the solutions were on opposite sides of a glass partition. But if the membrane happens to be semi-permeable, to allow water molecules but not the dissolved elements to pass through it (because the water molecules are smaller), then diffusion is impossible and the only way in which the solutions can tend to equalize their concentrations is by the osmosis of water. Under such conditions water moves through the membrane into the more concentrated solution, thereby increasing its volume. If this concentrated solution is in a closed container so that its volume cannot easily increase, an enormous osmotic pressure is set up, a pressure which will finally explode all but the strongest steel containers.

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GLOSSARY-INDEX

- ABSOLUTELY REFRACTORY STATE. *See* Refractory period.
- ABSORPTION. Taking up digested foods from the intestinal contents. 178, 194, 200, 201
- ACAPNIA. A cessation of breathing due to decreased carbon dioxide in the blood. 167
- ACCELERATOR NERVES. Orthosympathetic nerves to the heart which increase its beat. 76 (Fig. 32), 110, 111, 145
- ACETYL CHOLINE. A neurohumor liberated at parasympathetic nerve endings, and helping to transmit excitation. 75
- ACID. A substance which forms hydrogen ions in water solution. 8, 10, 20, 51, 83, 84, 85, 182, 184, 189, 190, 260
- ACTION POTENTIAL. The rapid electrical change which accompanies activity of a cell. 45, 46, 48, 48 (Fig. 25), 49, 64-65, 65 (Fig. 30), 66 (Fig. 31), 142
- ADAPTATION. Those changes in living material which better fit it for existence under the conditions in which it finds itself. Also, the decreasing response of a sense organ to a maintained stimulus. 66, 66 (Fig. 31)
- ADRENAL GLAND. An endocrine gland above the kidney with an outer cortex and inner medulla. 77, 85, 86 (Fig. 35), 118, 128, 166, 227, 228
- ADRENAL STIMULATING HORMONE. A pituitary hormone which maintains the normal state of the adrenal gland. 227
- ADRENALIN. A hormone of the adrenal medulla which stimulates orthosympathetic endings. Perhaps a neurohumor. 77, 85, 100, 118, 152, 157, 228, 254
- AFFECT. Emotion; sensory experience tinged with emotion. 253
- AFFERENT NERVE. A sensory nerve, leading impulses from receptors to the central nervous system. 42, 49, 65 (Fig. 30), 68, 78, 91, 111, 112, 163, 165, 180, 182, 235, 239, 246
- AFTERBIRTH. The placenta and fetal membranes. 221
- AGGLUTINATE. To cause clumping of small cells or particles. 214
agglutination tests, 215-216
- AGGLUTININ. An antibody which causes agglutination of bacteria. 215
- ALIMENTARY CANAL. The continuous passage of the digestive system, from mouth to anus. 177 (Fig. 65)
see also Digestive tract
- ALKALI. A base; the opposite of acid, producing hydroxyl ions when dissolved in water. 8, 19, 260
alkaline. 9, 10, 20, 189, 190
alkaline reserve, a measure of acid-neutralizing ability of the blood, 119
- ALLERGY. A mild type of anaphylaxis; such as hives, hayfever, or asthma. 217
- ALL-OR-NONE RELATION. That type of response to excitation in which the tissue acts to its fullest capacity or not at all. 18, 19, 31, 47-48, 48 (Fig. 25), 49, 50
- ALVEOLUS. A microscopic air sac of the lung, at the end of a bronchiole. 154, 154 (Fig. 54), 166, 167
alveolar air, 166, 167, 170

- AMINO ACIDS. Certain nitrogen-containing organic acids which combine in large numbers to form various kinds of protein molecules. 173, 189, 192, general 197-198, 259, 260
- AMMONIA. One end-product of the metabolic breakdown of nitrogen-containing food substances. 195
- AMNION. The embryonic membrane which forms a fluid-filled sac in which the embryo floats. 219, 220 (Fig. 80), 221
- AMYLOPSIN. The enzyme of pancreatic juice which digests starches. 192
- ANABOLISM. The building up, synthetic, aspect of metabolism. *Compare* Catabolism. 196
- ANEMIA. Decreased amount of blood or of red blood cells or hemoglobin. 152, 174, 198
- ANTIBODY. Immune body; enzyme-like substance liberated into the tissue fluids by phagocytic cells after digesting foreign proteins. 209, 210, 216, general 214-215, 217
- ANTIDIURETIC HORMONE. A hormone secreted by the pituitary which acts to decrease the volume of urine formed. 92, 201
- ANTIDROMIC. Conduction of an impulse along a nerve fiber in the direction opposite to that of normal travel. 49
- ANTIPERISTALSIS. Peristaltic movements of some part of the digestive tract which move the contents towards the mouth rather than towards the anus. 186
- ANTIPROTHROMBIN. A substance which prevents the change of prothrombin to thrombin as in normal blood clotting. 114, 115, 116
- ANTITHROMBIN. A substance which prevents the action of thrombin in changing fibrinogen into a fibrin clot. 114, 116
- ANTITOXIN. An antibody which acts upon bacterial toxins to render them ineffective. 216
- AORTA. The main arterial trunk of the body, which receives the blood from the left ventricle of the heart. 107, 108 (Fig. 37), 111, 131, 146, 148
aortic pressure, 131, 139 (Fig. 47), 140
aortic valves, 140, 142, 143, 143 (Fig. 44)
- APHASIA. Loss of the ability to give meaning to symbols, especially to written or spoken words. A result of injury to the association areas of the cerebral cortex. 236, 239 (Fig. 86)
- APNEA. Cessation of breathing, usually temporary. 165
- APPENDIX. A vestigial part of the large intestine of man. 206, 206 (Fig. 73)
- ARTERIES. The larger vessels which carry blood away from the heart to the tissues. 107, 109, 129, 131, 131 (Fig. 42), general 133-135, 138, 143
arterial pressure, 109, 112, 141 (Fig. 48), 150, 151
- ARTERIOLES. The smaller vessels formed by the branching of arteries and branching in turn to form capillaries. 107, 108 (Fig. 37), 109, 110, 118, 129, 150, 208
- ARTERIOSCLEROSIS. Hardening of the arteries. 134, 134 (Fig. 45), 143 (Fig. 49)
- ASSOCIATION AREA. Region of the cerebral cortex not directly connected with lower parts of the nervous system. Primary association areas are connected with projection areas; secondary association areas with other association areas. 236, general 239-241
- ATROPHY. Loss of size and often of structure of a body part as the result of disuse or of disease. 227
- ATROPINE. The active drug of belladonna, which paralyzes parasympathetic effectors. 77, 157
- AURICLE. The thin-walled chamber of each half of the heart into which the veins empty. 107, 108 (Fig. 37), 131, 139, 140, 142, 144, 145, 146
- AURICULO-VENTRICULAR VALVES. The valves separating auricles and ventricles. That

- on the right side, with three cusps, is called the tricuspid valve; that on the left, with two cusps, is the mitral. 133 (Fig. 44), 140, 142
- AUTOCATALYSIS. A type of catalyzed reaction in which more of the original catalyst is produced. general 213-214, 228, 249 (Fig. 89)
- AUTOLYSIS. The breakdown and digestion of dead cells or tissues by the action of their own enzymes. 209
- AUTONOMIC NERVOUS SYSTEM. The visceral or sympathetic or vegetative nervous system; that portion of the nervous system the cell bodies of which are distributed in ganglia among the viscera. 38, general 73-79, 90, 105, 106, 118, 166, 188, 255
 reactions of, 253-254
 see also Orthosympathetic; Parasympathetic
- A-V BUNDLE. The conducting bundle in the wall between the two ventricles which carries excitation from the A-V node to the ventricular muscle. 145, 146, 146 (Fig. 51)
- A-V NODE. Auricular-ventricular node; that portion of the conducting system of the heart, lying at the juncture of the right auricle and ventricle, which sets off the ventricular beat. 145, 146, 146 (Fig. 51)
- A-V VALVES. *See* Auriculo-ventricular valves
- AXIS CYLINDER. The long process of a neurone; a nerve fiber. 38
- AXONE. The axis cylinder, often surrounded by a layer of myelin. 37 (Fig. 19), 38, 39, 40, 41, 41 (Fig. 22), 52, 53, 55, 66, 75
- BACTERIA. 187, 204, 205 (Fig. 72), 206-208, 208 (Fig. 74), 209 (Fig. 75), 210, 211 (Fig. 76), 212-215
- BACTERICIDES. Bacteria-killing agents, mainly chemicals. 217-218
- BACTERIOLYSIN. An antibody which kills and dissolves bacteria. 215
- BASE. *See* Alkali
- BERI-BERI. A deficiency disease resulting from lack of vitamin B₁, with symptoms of paralysis and sometimes convulsions. 198
- BILE. Gall: the dark reddish-green fluid secreted by the liver. 116, 184, 186, general 192-194
 ducts, 173, 176, 192, 193
 salts, of complex organic acids present in bile and important for emulsifying fats preparatory to their digestion. 192, 193, 194
- BLOOD—and gas transport, 168-171
 arterial, 130, 131, 166, 167, 168, 169
 clotting, 112-117, 119, 198
 poisoning, 210-217
 rate of flow, 146-148
 regulation of composition, 87-101
 regulation of pressure; *see* Blood pressure
 regulation of temperature, 103-107
 venous, 130, 153, 167, 168
 see also Agglutination tests; Circulatory system; Plasma; Platelets; Red cells; White cells
- BLOOD PRESSURE, 81, 112, 135, 139 (Fig. 47), 141 (Fig. 48), 143 (Fig. 49), 149 (Fig. 53), 233
 and kidney, 200
 as related to flow, 148-150
 measurement of, 140, 141 (Fig. 48)
 regulation of, 107-112
 see also Arterial; Venous

BOIL, 208-210

BONE, 90, 93, 223, 225, 226 (Fig. 83)

see also Rickets

BONE MARROW. The non-bony fatty tissue in the inner cavities of bones, often a site of formation of blood cells. 171, 174, 175

BRAIN. Loosely used for all the central nervous system except the spinal cord, or for just the cerebral hemispheres. 38, 50, 51, 54, 62, 68, 69, 70, 72, 74, 87, 90, 92, 99, 104, 105, 110, 128, 151, 190, 225, 233 (Fig. 84)

and mind, 235-245

see also Segmental nervous system; Suprasegmental nervous system

BRAIN-STEM. The neuraxis; the more primitive segmental portion of the central nervous system, not including the cerebellum and cerebrum. 233 (Fig. 84), general 233-234, 245, 253

BRAIN WAVES. Feeble, fairly regularly repeated waves of potential change produced by the living brain. general 250-252

BRONCHIOLE. A fine respiratory tube ending in alveoli. 154, 154 (Fig. 54), 157

BRONCHUS. A main branch of the trachea or of one of these branches. 154, 154 (Fig. 55), 157, 213

BUFFER. A mixture of particular substances which tends to prevent marked changes in acidity or alkalinity. 90

CALCIFEROL. Vitamin D; necessary to normal bone development and calcification. 93, 94

CALCIUM CHLORIDE. A salt universally present in protoplasm. general 93-95, 225 ions, 116

CALORIE. A unit of heat; the amount of heat needed to raise the temperature of a gram of water by one degree. A large calorie is a thousand times as great. 104, 119, general 195-196

CANCER, 186, general 229-230

CAPILLARY. A fine tube. In the body, usually the finest vessels of the circulatory system. 82 (Fig. 33), 88, 107, 109, 110, 118, 129, 130, 131 (Fig. 42), 132, 147 (Fig. 52), 149 (Fig. 53), 150, 151, 153, 167, 170, 171, 198, 199, 200, 207, 208 (Fig. 74), 208, 210, 219

CARBOHYDRATE. A body constituent containing carbon, hydrogen, and oxygen in the proportions 1 : 2 : 1; a sugar or starch. 97, 192

see also Sugar

CARBON DIOXIDE, 22, 118, 119, 153, 163, 166, 195, 197, 198
exchange in the lungs, 166-171
regulation, 79-83

CARDIAC. Referring to the heart. 111

cycle, 138-142

output, the amount of blood pumped by the heart per beat (stroke output)
or per minute (minute output), 107-109, 118

see also Heart; Muscle

CAROTID. The main artery supplying the head, also other structures anatomically related to it, as the carotid body.

artery, 107, 111, 111 (Fig. 38)

chemoreceptor, 166

nerve, 111 (Fig. 38)

sinus, 151, 167, 233

CATABOLISM. The destructive, burning up, aspect of metabolism. Compare Anabolism. 196

- CATALYST. An agent, usually a substance, which accelerates a chemical reaction without being itself used up in the reaction. 213, 214, 228
- CATHEPSIN. A protein-digesting enzyme present in cells. Important in autolysis. 190
- CELL. The smallest unit of organized protoplasm capable of relatively unlimited survival. 1, 39, 53, 58, 72, 89, 95, 115, 130, 190, 219
 defense, 206-213
 metabolism, 79-81, 96, 103
 supercell, 4 (Fig. 3a), 6, 29, 30 (Fig. 16); *see also* Syncytium
 "typical," 5 (Fig. 3b)
see also Blood; Endothelium; Epithelium; Gland; Muscle; Neurone
- CENTRAL. Used as an antonym for peripheral in designating structures; the central end of a cut nerve would be the portion left attached to the nervous system rather than to some peripheral structure, the peripheral end.
- CENTRAL NERVOUS SYSTEM, 36, 49, 57, 66, 74, 76 (Fig. 32), 78, 79, 118, 128, general 232-235, 238 (Fig. 85)
- CEREBELLUM. Part of the suprasegmental nervous system concerned largely with the coordination of voluntary movement. 37 (Fig. 19), 233 (Fig. 84), 234, 247
- CEREBRAL CORTEX. The outer gray layer of the cerebrum, containing the cell bodies of the newest neurones. 37 (Fig. 19), 72, general 234-235, 236, 237, 239 (Fig. 86), 240 (Fig. 87), 247, 248, 255, 256, 257
- CEREBROSPINAL FLUID. The clear watery fluid in cranium and spinal column in which the central nervous system floats. 237
- CEREBRUM. The two cerebral hemispheres; often called the brain. 163, 188, 234, 237, 239, 247, 248, 250, 254, 256, 257
- CHEMOTAXIS. The influence of specific chemicals in directing cell growth or movement. 207.
- CHOLAGOGUE. A substance which stimulates the secretion of bile. 193
see also Bile salts
- CHOLECYSTOKININ. A hormone liberated from the intestine which helps to contract the gall bladder. 193
- CHORION. The outermost embryonic membrane, which contributes to formation of the placenta. 219, 220 (Fig. 80)
- CHYME. Fluid or semi-fluid intestinal contents. 184, 192
- CILIA. Microscopic thread-like extensions of a cell which cause movement by beating. 121, 157
- CIRCULATION, 81, 112
 failure of, 151-152
 proof of, 137-138
- CIRCULATORY SYSTEM, 108 (Fig. 37)
 general plan, 129-131
 lining of, 131-133
see also Arteries; Blood pressure; Capillaries; Heart; Veins
- CLOT. A coagulated mass. 113, 113 (Fig. 39), 131, 204
- COAGULATION. *See* Blood, clotting of
- COLLOID. An intermediate state of matter between a true solution and a particulate suspension; the physical state of protoplasm. 14, 113, 192, 200, 261
- COLON. The large intestine. 178-179 (Fig. 66), 184, 185 (Fig. 69), 186
- CONDITIONED REFLEX. An established habit; a reflex which is not inborn but has been acquired by the individual as a consequence of repeated experience. 188, general 248-250, 255, 256
- CONDUCT. *See* Propagate
- CONNECTIVE TISSUE. The binding tissue of the body, composed of fibroblasts and

- the elastic or tough fiber network produced by them 117, 131, 134, 160, 209, 209 (Fig. 75), 210
- CONSCIOUSNESS, 68, 253
and neural activity, 235-237
- CONTRACTION. The active response of a muscle, leading to shortening or to increased tension. general 4-25, 12, 14, 15, 14 (Fig. 19), 66, 140
all-or-none, 18, 19, 31
energy for, 9-11, 12, 20
gradation of, 15-16
in cardiac muscle, 29-31
in smooth muscle, 27-28, 29 (Fig. 15)
isometric, 13, 13 (Fig. 8), 14 (Fig. 9), 17
isotonic, 13, 14 (Fig. 9)
machinery of, 7-9, 20
organization for, 5-6, 12
summation of, 16-17
- CONTRACTURE. A maintained muscle shortening resulting from failure to relax rather than from continued stimulation to contract. 10-11 (Fig. 7), 11, 12
- CONVOLUTED TUBULE. A part of the secreting unit of the kidney, the nephron. 198, 199 (Fig. 71)
- COORDINATING MECHANISMS, 72-87
- CORONARY. The blood vessels which serve the heart muscle. 132
- CORPUS LUTEUM. The yellow mass on the ovary formed from the ruptured follicle after the egg is discharged. A temporary structure which forms several hormones important in the sex cycle. 124 (Fig. 41), 125, 126
see also Follicle, ovarian
- CORTEX. An outer mantle; usually the cerebral cortex if unspecified, but sometimes the adrenal cortex.
see Adrenal; Cerebral
- COUGH, 156, 159, 204
- CRAMP, 11, 204
- CRETIN. A deformed dwarf resulting from congenital thyroid deficiency. 223, 223 (Fig. 82)
- CYTOPLASM. The general bulk of cell protoplasm, excluding the nucleus or other special cell structures. 5 (Fig. 3*b*)
- DEFENSE—cellular, 206-213
chemical, 213-218
mechanical, 203-206
- DEGENERATION. Loss of normal structure and function, as in nerve fiber cut from its cell body. 39, 39 (Fig. 20)
- DENDRITE. A relatively short branching process of a nerve cell which receives impulses from other nerve cells. 37, 37 (Fig. 19), 41, 49, 66
- DEPOLARIZE. To discharge a pre-existing polarization; to have the opposite charges on the two sides of a membrane neutralize each other. 53, 54 (Fig. 27), 60
- DEPRESSOR NERVE. An afferent nerve from the heart and aorta which is stimulated by increased blood pressure and acts upon medullary centers reflexly to lower blood pressure. 111
- DIABETIS INSIPIDUS. A disease due to loss of the anti-diuretic hormone of the hypothysis. The dominant symptom is excretion of tremendous quantities of urine. 92
- DIABETES MELLITUS. The usual "diabetes," associated with decreased internal secretion by the pancreas and marked by an increased amount of sugar in the blood and its presence in urine. 100, 101

- DIABETOGENIC HORMONE. A pituitary hormone which tends to produce the disturbed sugar metabolism of diabetes. 100
- DIAPHRAGM, 155, 158, 159, 159 (Fig. 58)
- DIARRHEA, 186, 204
- DIASTOLE. The relaxation phase of the heartbeat. 30, 109, general 138-143
- DIT. *See* Food requirements
- DIFFERENTIATION, 224, 229
- DIGESTION, 83, 178
 chemical, 187-194
 mechanical, 178-187
- DIGESTIVE—juices, 188; *see also* Enzymes
 system, general 176-179
 tract, 155, 156, 157; *see also* Alimentary canal
- DILATION. Dilatation; increase in caliber of a hollow viscus. 80, 81, 82 (Fig. 33), 105, 110, 208
- DIPHTHERIA. A disease, attended by paralysis and heart failure, caused by the diphtheria bacillus and its powerful toxin. 216, 217
- DORSAL. On the backbone side of an animal; in contrast to ventral, on the bottom or belly side. 40
- DUODENUM. The upper foot or so of small intestine which receives the bile and pancreatic juices and secretes its own digestive fluid. 84, 176, 178-179 (Fig. 66), 182, 184, 189, 191, 192, 193
- DYSENTERY. A disease, caused by the dysentery bacillus, attended by diarrhea and other intestinal disturbances. 215
- EAR, 71
- EDEMA. Dropsy; the accumulation of excessive quantities of watery fluid in the tissues, especially under the skin. 92, 136, 151, 209
- EFFECTOR. A cell or organ which acts for the body, as muscle for movement and glands for chemical manufacture. 1, general 1-31, 36, 77, 228
 see also Gland; Muscle
- EFFERENT NERVE. A motor nerve, conducting impulses from the central nervous system to an effector. 49, 66, 78, 118, 180, 240, 245, 246, 247
- EGG. *See* Ovum
- ELECTROCARDIOGRAM. A record of the electrical changes produced in the body in the course of the heartbeat. 142, 144 (Fig. 50)
- EMBRYO. The early stage in development of an individual. The older human embryo is called a fetus. 123, 219, 220 (Fig. 80), 221, 222
- EMOTION, 118, 120, 127, general 253-257
- ENDOCRINE. Having to do with internal secretions; substances discharged into the blood stream rather than into special ducts which ultimately lead to the body surface.
 gland, 33, 85, 86 (Fig. 35), 87, 90, 128, 223
 see also Adrenal; Liver; Ovary; Pancreas; Parathyroid; Pineal; Pituitary; Placenta; Testes; Thymus; Thyroid
- ENDOTHELIUM. A lining layer of flat saucer-like cells which form a smooth moist membrane. 131, 131 (Fig. 42), 132, 133, 133 (Fig. 44), 172, 198, 207, 208 (Fig. 74), 208, 220 (Fig. 80), 221
- ENERGY, 22, 23, 33, 103, 195
 for contraction, 9-11, 12, 20
- ENTEROGASTRONE. A hormone, liberated from the duodenum by fats, which inhibits stomach movements. 192

- ENTEROKINASE. A substance secreted by the duodenum into its cavity, where it meets and renders active the trypsin in pancreatic juice. 192
- ENZYM. A highly efficient and specific catalyst formed by living cells; probably always containing protein. 33, 83, 190, 192, 213, 214
see also Amylopsin; Erepsin; Pepsin; Proteolytic; Ptyalin; Steapsin; Trypsin; Trypsinogen
- EPIDERMIS. Outer skin the many-layered epithelial covering of the body surface. 210, 212, 225, 229
- EPIDIDYMI. The long, highly coiled duct which carries spermatozoa away from the testicle. 218 (Fig. 79), 219
- EPIGLOTTIS. The cartilaginous flap above the larynx which closes off this passage during swallowing. 155, 155 (Fig. 56), 156
- EPITHELIUM. A covering sheet of cuboidal or columnar cells one or several layers thick. 157, 176, 184, 190, 198, general 203-204, 205 (Fig. 72)
- EREPSIN. A protein-digesting enzyme secreted by the duodenum. 189, 192
- ERYTHROCYTE. A red blood cell. *See* Red cell
- ESOPHAGUS. The gullet; the passage from mouth and pharynx to stomach. 155 (Fig. 56), 156, 178 (Fig. 66), 180, 182
- ESTRIN. A hormone secreted by the ovary which acts mainly upon the mucous membrane of the uterus. 123, 126, 127
- ESTRUS CYCLE. The regularly repeated changes which occur in the sex organs of the adult female in woman the menstrual cycle. 120-128
- EVOLUTION, 67, 71, 156, 171, 216, 221, 234, 237, 241, 248
- EXCITATION. The state brought about in a cell or tissue by a stimulus. When sufficient excitation is produced an active response results. 47, 54, 55
 mechanism of, 59-61
- EXCRETION. 184, 186, 198-201
- EXPIRATION. Breathing out; exhaling. 157, 158 (Fig. 57), 159, 159 (Fig. 58), 161, 163, 165
- EXTENSOR MUSCLE. A muscle attached across a joint in such position that the joint is straightened out by its contraction. Compare Flexor. 2 (Fig. 1), 12, 75
- EXTEROCEPTOR. A sense organ receiving stimuli from outside the body, as the eye or skin receptors, and including taste and touch receptors in the mouth. 64 (Fig. 29), 68
- EXTRASYSTOLE. A heart beat which occurs before the proper time; a premature beat. 30, 30 (Fig. 17), 144
- EYE, 59, 61, 62, 67, 71, 225, 236, 241
- FAINTING, 151, 152, 237
- FAT, 190, 195, 196
- FATIGUE, 10-11, 11 (Fig. 7), 12, 19
- FATTY ACID. The acid constituent of a fat. Usually three of these are combined with glycerin to make a fat molecule. 192
- FEMALE, 126, 127, 218, 229
 reproductive system, 121 (Fig. 40)
- FERMENTATION. Glycolysis; the metabolic breakdown of carbohydrate in the absence of oxygen; lactic acid and alcohol are the most important products. 21, 22, 24
- FETUS, 123, 161; *see* Embryo
- FIBR. A threadlike structure. In connective tissue several types are distinguished, of which one is elastic. 113, 117, 131 (Fig. 42), 209 (Fig. 75)
 muscle, 6, 7 (Fig. 4), 29, 66
 nerve, 38, 41 (Fig. 22), 46, 49, 54 (Fig. 27), 57, 61, 62, 63, 65
see also Blood, clotting of

- FIBRIN.** A protein which forms in blood in interlacing fibers to produce a clot. 116
formation of, 113-114
- FIBRINOGEN.** A protein of blood plasma which is changed to fibrin by the action of thrombin in the course of clotting. 113, 114, 116
- FIBROBLAST.** A connective tissue cell which produces the various connective tissue fibers and into which macrophages can change. 117, 209 (Fig. 75)
- FLXOR MUSCLE.** A muscle attached across a joint in such position that the joint is bent by contraction. Compare Extensor. 2 (Fig. 1), 75
- FOLLICLE.** A fluid-containing vesicle; usually the ovarian follicle which contains a ripening egg.
ovarian, 121, 123, 124 (Fig. 41), 124, 126
- FOLLICLE-STIMULATING HORMONE (FSH).** A hormone secreted by the pituitary gland which brings about the development of ovarian follicles. general 122-123, 126
- FOOD—absorption,** 194
excretion of wastes, 184, 186 198-201
requirements, 195-198
see Digestion
- GALL BLADDER.** A bladder, branching from the main bile passage from liver to duodenum, which stores and concentrates bile. 116, 173, 178 (Fig. 66), general 192-194
- GALL STONES,** 192
- GANGLION.** A small swelling; specifically a small mass composed of the bodies of neurones. 74, 75, 76 (Fig. 32), 78, 228
- GANGRENE.** Death of large tissue masses, associated with interrupted blood supply and infection. 132.
- GASTRIC.** Referring to the stomach.
juice, 83, 182, 187, general 189-190
control of, 190-192
ulcer, 190, 204, 229, 255
see Pavlov pouch
- GASTRIN.** A substance of endocrine character, liberated from the stomach and duodenum, which leads to gastric secretion. 191
- GASTROCNEMIUS.** The calf muscle which extends the ankle, as in rising on the toes. 11, 26, 27, 26 (Fig. 12), 42
- GEL.** The semi-solid jellied state of a colloid. Compare Sol. 113, 261
- GIGANTISM.** Overgrowth in height and weight due to excessive pituitary action in childhood. 223 (Fig. 82), 224
- GLAND.** A chemical effector which concentrates blood substances in its secretion or manufactures entirely new ones. 1, 31-34, 54, 57, 84, 86 (Fig. 35), 176, 177 (Fig. 65), 190, 227
which concentrates, 31-32
which manufactures, 32-34
see also Endocrine; Gastric; Lymph; Mammary; Pancreas; Prostate; Salivary; Sweat
- GLOMERULUS.** The tuft of capillaries through which blood fluid filters at the start of urine formation. Part of the nephron. 198, 199, 199 (Fig. 71), 200, 201
- GLUCONOLOGNESIS.** The new formation of glucose from protein or other non-carbohydrate substances, especially in the liver. 101
- GLUCOSE.** Grape sugar; the most important food molecule. 21, 118, 228
origin of, 100-101
regulation of, 96-100
see also Glycogen; Sugar

- GLYCOGEN.** Animal starch; an insoluble storage form of carbohydrate formed by the combination of many glucose molecules. 21, 23, 97, 100, 101, 118, 228
see also Glucose; Sugar
- GLYCOGENOLYSIS.** The breakdown of glycogen to glucose, especially in the liver. 100
- GLYCOLYSIS.** *See* Fermentation
- GOITER.** A swelling in the neck due to enlargement of the thyroid gland. 94, 227
- GONAD.** A sex gland, either ovary or testis. 86 (Fig. 35), 121 (Fig. 40), 218 (Fig. 79), 227
- GRANULOCYTE.** The granule-containing white blood cells formed in bone marrow.
 Contrast Lymphocyte. 210
- GRAY MATTER.** The gray-appearing portions of the central nervous system, containing the cell bodies of neurones. 38, 39 (Fig. 20), 40 (Fig. 21), 41 (Fig. 22), 239
- GROWTH,** 196, 214, 218, general 221-230, 222 (Fig. 81), 249, 250
- GROWTH-STIMULATING HORMONE,** 223
- HEART,** 56, 75, 108 (Fig. 37), 110, 112, 119, 129, 130, 131, 133, 133 (Fig. 44), 146 (Fig. 51), 148, 200
see also Cardiac
- HEART BLAT,** 30 (Fig. 17), 109, 110, general 138-144, 163
 control of, 144-146
- HEAT,** 208
 and energy, 22-23, 195
 loss, 104-107, 120
 production, 103-104, 118
- HEMOGLOBIN.** The oxygen (and carbon dioxide) carrying red pigment of blood.
 and oxygen, 168-171
 in the red cell, 171-175
- HEMOPIHILIA.** An inherited disease in which blood coagulation is slow or absent. 116
- HOMIOSTASIS.** Self-regulation; the body processes for maintaining various blood and other conditions constant at the proper level. Chapters 3 and 4, 90, 117
- HORMONE.** A specific physiologically active substance secreted by an endocrine gland. 33, 83, 85, 86 (Fig. 35), 87, 218
see also Adrenal; Adrenalin; Adrenal-stimulating hormone; Carbon dioxide; Cholecystokinin; Antidiuretic; Diabetogenic; Enterogastrone; Estrin; Follicle-stimulating hormone; Gastrin; Growth-stimulating hormone; Insulin; Luteinizing hormone; Male sex hormone; Parathormone; Pituitary; Progesterone; Progestin; Secretin; Thyroid; Thyroxin
- HUNGER,** 104, 182, 183, 183 (Fig. 68), 195
- HYDROCEPHALUS.** Swelling of the skull and compression of the brain by excessive cerebrospinal fluid. 237
- HYDROCHLORIC ACID,** 182, 189
- HYDROXYL.** The ion characteristic of an alkali; the OH^- ion. 260
- HYPERGLYCEMIA.** Increase in amount of blood sugar above the normal level. 101
- HYPERPNIA.** Increased rate or depth of breathing. 165
- HYPERTROPHY.** Increase in weight of an organ, mainly as a consequence of its normal functioning. 143, 205 (Fig. 72), general 225-227, 228, 229
- HYPOLYCEMIA.** Decrease in the amount of blood sugar below the normal level. 99
- HYPOPHYSIS.** Pituitary; the three-lobed endocrine gland at the base of the brain which helps regulate the activity of most other endocrine glands. 86 (Fig. 35), 87, 92, 95, general 100-101, 122, 123, 126, 127, 128, 223, 224, 227, 229
see also Pituitary
- HYPOTHALAMUS.** The under part of the thalamus; the primitive front end of the segmental nervous system. 79, 92, 99, 106, 118, 223 (Fig. 84), 256

- IMMUNITY.** A state of being resistant to a particular disease as the result of previous infection or vaccination (active immunity) or as a result of the injection of antibodies (passive immunity). 215 (Fig. 78), general 216-217
- INFECTION.** 206, 207, 208 (Fig. 74), 209, 247
- INFLAMMATION.** The active reaction of tissues to infection or other continued irritation, attended by vasodilation and edema. general 208-210, 229
- INHIBIT.** To hold in check, to repress, or to decrease or stop a pre-existing state of activity. 55, 56 (Fig. 28), 75, 76, 80, 83, 104, 110, 111, 114, 127, 145, 156, 182, 192, 245, 246, 254
- INSANITY.** 237, general 254-255
- INSPIRATION.** Inhaling, breathing in. 157, 158 (Fig. 57), 159, 159 (Fig. 58), 161, 163, 165
- INSULIN.** The hormone, produced by the islands of the pancreas, which helps control sugar metabolism. 87
control of, 99-100
role of, 98-99
- INTELLIGENCE.** 235, 247, 254
measuring, 241-245, 250
and emotion, 255-257
- INTERCOSTAL MUSCLES.** The muscles attached between adjacent ribs, which lift the chest in inspiration. 155, 157
- INTERCOSTAL NERVES.** The nerves running from the upper spinal cord to the intercostal muscles. 157
- INTERNAL ENVIRONMENT.** 88, 129
constancy, chemical, 87-102
constancy, physical, 103-117
see also Milieu interieur
- INTEROCEPTOR.** A sense organ receiving stimuli from within the body, as those in the stomach which signal hunger. 68, 78, 111
- INTESTINE.** 118, 173, 173 (Fig. 66), 186, 213
large, 184, 185 (Fig. 69)
small, 176, 177, 185 (Fig. 69)
see also Digestive tract; Duodenum
- INTRAVENTRICULAR PRESSURE.** The pressure of the blood within a ventricle, usually the left one. 139 (Fig. 47), 140
- IODINE.** 188, 227
- ION.** The charged fragment of a molecule produced when it dissociates in water solution. 53, 60, 93, 95, 116, 260, 261
- I.Q.** Intelligence quotient; the ratio of mental age to chronological age. 243, 244
- ISOMETRIC.** Constant length; the contraction of a muscle when it is prevented from shortening and instead develops tension. 13, 14 (Fig. 9)
- ISOTONIC.** Constant tension; the contraction of a muscle allowed to shorten and lift a constant load. 13, 14 (Fig. 9)
- KIDNEY.** The main organ of excretion, it discharges soluble wastes in the urine. 32, 91, 92, 95, 130, 197, 199 (Fig. 71), 221
excretion by, 198-201
- KNEE JERK.** The reflex extension of the leg at the knee, elicited by stretching the extensor muscle by tapping its tendon. A stretch reflex concerned in posture. 245
- LACTATION.** The secretion of milk by the breasts of a recent mother. 229
- LACTIC ACID.** The main product of sugar fermentation in the animal body; especially important in muscle contraction. 21-24, 80, 119

- LARYNX.** The voice box. 154-156
- LEARNING,** 221, 234-235, 248, 249, 250
- LESION.** A region of injury or destruction of a tissue or organ; a burn is a lesion of the skin. 236
- LEUCOCYTE.** White blood cell. 208, 208 (Fig. 74), 209 (Fig. 75), 215
see Granulocyte; Lymphocyte; Phagocyte
- LIPID.** A fat or fat-like substance. *See* Fat
- LIVER.** The main chemical factory of the body, concerned in the digestion and metabolism of food. 32, 85, 97, 98, 100, 108 (Fig. 37), 112, 115, 116, 130, 172, 173, 172 (Fig. 64), 189, 193, 194, 196, 210, 228
- LUMEN.** The cavity of a hollow viscus. 199, 201
- LUNG.** The organ for exchanging oxygen and carbon dioxide between blood and air. 108 (Fig. 37), 119, 130, 153, 154, 155, 154 (Fig. 55), 156, 157, 160-162
 gas exchange in, 166-168
see Respiration
- LUTEINIZING HORMONE.** A pituitary hormone which helps change a ruptured ovarian follicle into the corpus luteum. 126
- LYMPH.** The fluid, formed from blood plasma, which filters between tissue cells, then through lymphatic channels, and is finally emptied into veins. 88, 210, 214, 230
see Lymphatics
- LYMPH GLAND OR NODE.** Special filtering structure through which lymph channels pass. Site of formation of lymphocytes. 88, 172 (Fig. 64), 207, 211 (Fig. 76), 212 (Fig. 77)
see Lymphatics; Tonsils
- LYMPHATICS.** The lymph vessels and channels. general 210-213
- LYMPHOCYTE.** A non-granular white blood cell, formed in lymph nodes and carried into the blood. Contrast Granulocyte. 88, 207, 211 (Fig. 76)
- MACROPHAGE.** Large phagocytic cell; present as part of the reticulo-endothelial system in tissues or formed in them from lymphocytes. 117, 172 (Fig. 64), 207, 209, 209 (Fig. 75), 210, 211 (Fig. 76)
see also Phagocyte
- MALE,** 127, 128, 218, 229
 reproductive system, 218, 218 (Fig. 79)
 sex hormones, 127
- MAMMARY GLAND.** Breast. 120, 123, 126, 221, 229
- MANOMETER.** An instrument for measuring pressure. 140
- MAXIMAL RESPONSE.** The greatest response a tissue is able to give under existing conditions; not necessarily the greatest response of which it is capable. 16, 17, 17 (Fig. 11), 19, 48, 163
- MEDULLA.** An inner core; usually referring to the oblong portion of the brain stem (medulla oblongata, really), if unspecified; sometimes the medulla of the adrenal gland. 79, 82, 110, 111, 112, 157, 186, 188, 233 (Fig. 84), 234, 246
see Adrenal, for adrenal medulla
- MENINGES.** The membranes covering the brain, including the delicate pia mater and the tough outer dura mater. 232
- MENOPAUSE.** The normal cessation of the menses at "change of life." 121
- MENSTRUATION.** *See* Estrus cycle
- METABOLISM.** The sum total of chemical changes in the living body; including building up processes, anabolism, and breaking down processes, catabolism. 32, 46, 49, 53, 96, 118, 150, 195, 196-198, 214, 228, 237, 261
 basal, 104, 195

- METABOLISM (*Continued*)
 muscle, 20-25, 79-81
 see also Anabolism; Catabolism
- MICELLE. An elongated submicroscopic particle. 6, 7 (Fig. 4), 9 (Fig. 6), 261
- MICROPHAGE. A small phagocytic cell, such as a granulocyte. 207, 208 (Fig. 74), 209 (Fig. 75)
 see also Granulocyte; Lymphocyte; White cell
- MIDBRAIN. The portion of the brain stem below the thalamus and above the medulla and pons. 233 (Fig. 84), 234, 247
- MILIEU INTERIEUR. The internal environment; the constant conditions of temperature, chemical composition, and the like of the tissue fluids which bathe individual cells. *See* Internal environment
- MIND, general 234-245
- MOTOR. *See* Efferent
- MOTOR AREA. That projection area of the cerebral cortex which discharges the nerve impulses leading to voluntary motion. 239 (Fig. 86), 240, 240 (Fig. 87)
- MOTOR UNIT. A motor spinal neurone, its nerve fiber, and the muscle fibers it innervates. 66
- MOUTH, 188, 205 (Fig. 72), 213
- MUCOUS MEMBRANE (MUCOSA). The slippery mucus-secreting epithelium lining the digestive system and other cavities open to the body surface. 28 (Fig. 14), 123, 124 (Fig. 41), 124-126, 155-157, 177, 179 (Fig. 66), 187, 188, 190, 205 (Fig. 72), 207, 219
- MUSCLE. The main effector of the body; almost the only tissue producing movement. 1-31, 43, 44 (Fig. 23), 50, 54, 57, 69, 90, 104, 178, 241
 cardiac, 29-31, 56
 functions of, 25-26
 metabolism of, 20-25
 smooth, 27-29, 57
 striated, 3, 4 (Fig. 3a), 29, 30 (Fig. 16), 225
 see also Fiber, muscle
- MYELIN. The fatty insulating material which forms a sheath on many nerve fibers. 38, 39 (Fig. 20), 39
- MYONEURAL JUNCTION. The specialized region at which a nerve fiber connects to the muscle fiber it innervates. 55
- NEPHRITIS. Acute or chronic disease of the kidney attended by interference with urine formation. 92, 96, 197
- NEPHRON. The functional and structural unit for urine formation. 198, 199, 199 (Fig. 71), 200
- NERVE. A bundle of nerve fibers or axones running between the central nervous system and some peripheral structure. 33, 51-52, 61, 224, 233, general 36-42
 see also Afferent; Autonomic; Efferent; Fiber, nerve; Neurone
- NERVE IMPULSE. The message which travels along the nerve fiber and produces excitation. general 42-54, 52 (Fig. 26), 54 (Fig. 27), 59, 65, 66, 66 (Fig. 31), 68, 70, 118, 235
 electrical changes in, 43-44
 neural activity and consciousness, 235-237
 propagation of, 42-57
 velocity of, 43-46
- NEURAXIS. *See* Brain-stem. 233 (Fig. 84), 234, 235
- NEUROHUMOR. A chemical, or humoral, agent produced at nerve endings and helping to transmit excitation from a nerve fiber to an effector or another nerve cell. 56 (Fig. 28), 57

- NEURONE. A nerve cell. 28, general 36-38, 39-41, 40 (Fig. 21), 49, 55, 66, 74, 78, 225, 234, 235, 250, 252
- NEUROSIS. A functional disturbance in behavior or attitude, usually resulting from disturbing early experiences. general 254-255
- NEUROSIS, ORGAN. Malfunctioning of an organ, resulting originally from emotional or other psychic disturbances; gastric ulcer may be an example. 255
- NITROGEN, 101, 196-197, 201, 259
balance. The comparison between the amounts of nitrogen entering the body in foods and leaving it in wastes. 196
- NODAL TISSUE. The specialized tissue in the heart which conducts to the cardiac muscle the excitation to beat. 145, 146 (Fig. 51)
- NOSE, 155 (Fig. 56), 156-157, 213
- NUTRITION—absorption of foods, 194
food requirements, 195-201
- OCCIPITAL. Referring to the back portion of the head or brain. 241, 243 (Fig. 88)
- OMENTUM. A fold of peritoneum hanging in front of the abdominal viscera. 204-206
- OPSONIN. An antibody which facilitates phagocytosis. 215
- ORTHOSYMPATHETIC. The "straight" division of the autonomic nervous system which connects with the middle and upper spinal cord. In opposition is the parasympathetic division. 55, 57, 76 (Fig. 32), 99, 100, 106, 110, 118, 157, 228, 253, general 74-78
- OPTIC NERVE. The nerve carrying visual sensations from eye to brain. 59, 66, 66 (Fig. 31)
- OSMOSIS. The movement of water through a semi-permeable membrane from a solution containing less dissolved material into one containing more. 261, 262
- OSMOTIC PRESSURE. The pressure, often considerable, developed by water in the course of osmosis. 24, 92, 96, 151
- OVARIAN HORMONE. *See* Estrin and Progesterin
- OVARY. The female gonad or sex organ which forms eggs and some hormones. 85, 87, 120, 121, 121 (Fig. 40), 123, 124, 124 (Fig. 41)
- OVIDUCT. The open tube along which the mature (or fertilized) egg slowly travels from the ovary to the uterus. 120, 219
- OVULATION. The release of a mature egg from an ovarian follicle when this latter ruptures. 121, 124, 124 (Fig. 41), 126
- OVUM. An egg. 120, 123, 124 (Fig. 41), 126, 219
- OXIDATION. The change of a molecule produced by adding oxygen or losing hydrogen atoms. (More rigorously, the loss of electrons) 21, 22, 24, 52, 195
- OXYGEN. The gaseous element vital for cell respiration and an attendant liberation of energy for work. 80, 81, 85, 118, 153, 175, 259
"debt." The accumulated need for extra oxygen by a muscle which has formed an excess of lactic acid during vigorous contraction. 24, 80, 119
dissociation curve, 120 (Fig. 63)
exchange in the lungs, 166-171
- OXYHEMOGLOBIN. A compound formed by the loose combination of oxygen with hemoglobin; the means of transport of this gas in the blood. 169, 170 (Fig. 63)
- PACMAKIR NODE. The bit of nodal tissue in the heart, lying in the wall of the auricle, from which each normal heart beat originates. 145, 146, 146 (Fig. 51)
- PANCREAS. A gland, lying below the stomach, which secretes digestive juice into the duodenum and the hormone insulin into the blood. 32, 83, 84, 85, 87, 99, 100, 101, 188, 189

- PANCREATIC JUICE. The digestive secretion of the pancreas, containing alkali and digestive enzymes. 85, 184, 189, general 192
duct, 176
- PARALYSIS. A blocking of normal function; particularly applied to loss of the ability to contract a muscle. 132, 198
- PARAMECIUM. A ciliated protozoan. 89
- PARASYMPATHETIC. The "opposing" portion of the automatic nervous system, connected to the central nervous system at the upper brain stem and lower spinal cord, which acts oppositely to the orthosympathetic division. general 74-78, 99, 110, 118, 120, 157, 182
- PARATHORMONE. The hormone secreted by the parathyroid gland which helps regulate calcium metabolism. 94
- PARATHYROID. Four small endocrine glands, embedded in the thyroid, which produce parathormone. 85, 86 (Fig. 35), 94, 95
- PAVLOV POUCH. A pouch from part of the stomach which permits pure gastric juice to flow to the body surface. 191 (Fig. 70)
- PELLAGRA. A deficiency disease resulting from lack of the B group of vitamins and marked by blackened sores of the skin and mouth. 198
- PEPSIN. The protein-digesting enzyme secreted by the stomach. 189, 191
- PERICARDIUM. The infolded endothelial sac around the heart, which allows this to move freely in the surrounding tissues. 133 (Fig. 44), 154
- PERIPHERAL, 38
see Central.
- PERIPHERAL RESISTANCE. The collective resistance offered by arterioles and capillaries to the onward flow of arterial blood. 149 (Fig. 53), 150
- PERISTALSIS. Peristaltic motion; a characteristic movement of tubular hollow viscera, especially the alimentary tract, characterized by a slowly advancing wave of constriction which is often preceded by one of relaxation. 28, 29 (Fig. 15), 156, 177, 180, 181 (Fig. 67), 182, 183 (Fig. 68), general 184-185, 204
- PERITONEUM. The closed much-folded endothelial membrane covering the abdominal viscera and the walls of the abdominal cavity. 204, 206 (Fig. 73), 213
- PERSPIRATION, 106, 107
- PHAGOCYTE. A cell which engulfs and digests particulate matter. 172 (Fig. 64), 206, general 207-208, 208 (Fig. 74), 209, 209 (Fig. 75), 211 (Fig. 76), 212, 213, 214
see Macrophage, Microphage, White cell
- PHAGOCYTOSIS. The process of taking up particles by a phagocyte. 172
- PHARYNX. The back of the mouth cavity and its walls. 155 (Fig. 56), 156, 157, 180
- PHRENIC NERVE. The nerves running from the upper spinal cord, one on each side of the heart, which make the diaphragm contract. 158
- PINEAL. A small structure lying above the thalamus and possessing some endocrine function. 85, 224
- PITUITARY. *See* Hypophysis
gland, 85, 222
see also Antidiuretic hormone; Adrenal-stimulating hormone; Diabetogenic hormone; Follicle-stimulating hormone; Growth-stimulating hormone; Luteinizing hormone; Thyroid-stimulating hormone
- PLACENTA. Afterbirth; a special organ formed from the uterine mucosa and the chorion for nourishing the developing infant. 85, 125, 126, 219, 220 (Fig. 80)
hormone; *see* Progesterone
- PLASMA. The fluid portion of normal unclotted blood. Compare Serum. 88-90, 95, 112, 113, 167, 168, 200, 201, 209, 214, 215, 215 (Fig. 78), 216

- PLATELET.** A formed element of the blood, smaller than the blood cells and with no nucleus, which breaks down to initiate clotting. 115, 116
- PLEURA.** The infolded double endothelial sac surrounding the lung and lining the chest wall. There is a separate one for each lung. 154 (Fig. 55), 155, 160, 161
- PLEXUS.** An interlacing network of elongated structures, as of blood vessels in the choroid plexus or of nerve fibers in the nerve plexus of the arm or leg. 75, 182
solar, 79
- PNEUMOGRAPH.** An instrument for recording breathing movements. 164 (Fig. 61)
- PNEUMONIA,** 167, 217
- PNEUMOTHORAX.** The presence of considerable gas in a pleural cavity. 160 (Fig. 59), 160
- POLARIZE.** To produce a potential across a system, as when charges of opposite kinds accumulate on the two sides of a membrane. 53, 54 (Fig. 27)
- PORTAL VEIN.** The vein formed from the junction of capillaries in the intestine and in the spleen and which again breaks up into capillaries in the liver. 108, 108 (Fig. 37)
- POTASSIUM REGULATION,** 95
- PRECIPITIN.** An antibody which coagulates and precipitates proteins. 215 (Fig. 78), 216
- PREGNANCY,** 93, 95, 121, 125, 221
- PREMATURE BEAT.** *See* Extrasystole.
- PRESSOR NERVE.** Afferent nerves to the medullary centers which reflexly increase blood pressure. 112
- PROENZYME.** An inactive form in which many enzymes are secreted, to be changed at their place of action into the active enzyme. 192
- PROGESTERONE.** A placental hormone which inhibits lactation. 126
- PROGESTIN.** An ovarian hormone which helps induce the premenstrual changes of the uterine mucosa. 125, 126, 127
- PROJECTION AREA.** A region of the cerebral cortex directly connected with lower parts of the brain. Compare Association area. 239, general 239-241, 239 (Fig. 86)
- PROPAGATE.** Conduct; transmit; pass on; carry an impulse. 36, 46, 46 (Fig. 24), 152 (Fig. 26), 54 (Fig. 27)
- PROPRIOCEPTOR.** A sense organ in muscle or joint, the impulses from which contribute to the reflex control of movement. 69, 70, 104, 245, 246
- PROSTATE.** A glandular structure in the male reproductive system; its secretion helps carry the spermatozoa. 218 (Fig. 79), 219
- PROTEIN.** Albumin; a very large nitrogen-containing organic molecule built of amino acids. Various proteins are present in all protoplasm. 188-190, 192, 195, 196, 197, 200, 214, 261
molecule, 6, 7-10, 18, 19, 84, 189, 259
- PROTOLYTIC.** Protein-digesting. 190
see also Cathepsin; Pepsin; Trypsin; Erepsin
- PROTHROMBIN.** The precursor of thrombin normally present in blood plasma. 114-117
- PROTOPLASM.** An ill-defined term referring to the semi-fluid substance of which cells are composed. 9, 261
- PSYDOAFFECTIVE STATE.** The exaggerated, seemingly emotional, behavior of the thalamic animal. 254
- PTYALIN.** The starch-digesting enzyme of saliva. 188, 192
- PUBERTY.** The stage of development leading to sexual maturity. 120, 122, 123, 227
- PULMONARY.** Referring to the lung. 108, 162

- PULSE** A rhythmic change in quantity; especially the regular rise and fall in blood pressure and the associated movement of the arteries. 109, 141 (Fig. 48), 142-143
 pressure. The difference between systolic and diastolic pressure. 143 (Fig. 49)
- PUS.** The semi-fluid matter in a "ripe" boil, formed by the broken down bodies of bacteria and leucocytes. 206, 208-210
- PYLORIC SPHINCTER.** The heavy circular band of smooth muscle at the junction of stomach and duodenum. 179 (Fig. 66), 181 (Fig. 67), 181, 182
 control of, 182-184
- RECEPTOR.** A sense-organ or cell especially sensitive to a particular kind of stimulus. 57, 61-67, 69-71, 79, 119, 156, 165, 180, 188, 190, 209
 distance, 67-68
 see also Sense organ
- RECEPTOR-NEURAL JUNCTION.** The region of junction between a receptor cell and its afferent nerve fiber. 55
- RECTUM,** 184, 185 (Fig. 69)
- RED CELL.** Red blood cell; erythrocyte. 82 (Fig. 33), 115, 150, 207
 formation, 174-175
 see also Hemoglobin
- REDUCTION.** The reverse of oxidation. 52.
- REFLEX.** A coordinated response by effectors to a stimulus to a receptor, mediated through two or more neurones. 79, 104, 111, 156, 180, 182, 186, 193, general 204, 219, 235
 arc, 4 (Fig. 22), 78
 behavior, 42, 233-234, 245-250, 253
 see also Conditioned reflex
- REFRACTORY PERIOD OR STATE.** The brief interval following one response during which a cell cannot be reactivated at all (absolutely refractory period) or only with an excessively strong stimulus (relatively refractory period). 10, 30, 48-49, 53
- REGENERATE** To return to or towards the normal after injury; especially the outgrowth of new nerve fibers. 40
- RELATIVELY REFRACTORY PERIOD OR STATE.** *See* Refractory period, 49
- RELAXATION.** The passive decrease of tension or shortening which terminates an active contraction. 9, 9 (Fig. 6), 11, 12, 14 (Fig. 9), 28-30, 49, 140, 159
- RENAL—artery,** 108 (Fig. 37), 199
 vein, 199
- RENAL TUBULE.** A portion of the nephron, which is the urine-secreting element of the kidney. 198-199, 199 (Fig. 71)
- REPRODUCTION,** 121 (Fig. 40), 214, general 218-221, 218 (Fig. 79), 222 (Fig. 80)
- RESPIRATION,** 33, 49, 81, 82, 164 (Fig. 61), 165 (Fig. 62)
- RESPIRATORY CENTER.** The nerve cells in the medulla which discharge the nerve impulses responsible for coordinated inspiration. 119, 156-158, 163, 165-167
- RESPIRATORY SYSTEM,** 153-157
- RESPONSE.** The specific physiological active behavior of a cell or organ which follows an effective stimulus. 17, 19, 42, 47, 48, 50, general 58-61
 all-or-none, 17, 19, 47-50
- RETICULO-ENDOTHELIAL SYSTEM.** Phagocytic and endothelial cells composing a functional system but lying scattered about in other tissues. 172-174, 206, 210, 211 (Fig. 76)
- RETINA.** The layer of light-sensitive structures and of nerve cells lining the back of the eyeball. 62, 71, 225

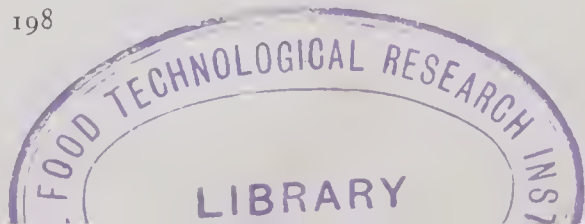
- RYTHM**, 28, 29 (Fig. 15), 127, 145, 146, 163
 biological, general, 122
- RHYTHMIC SEGMENTATION**. Contraction rings which appear simultaneously at intervals along the duodenum but do not move along. 184
- RIBS**, 155, 157, 158 (Fig. 57), 159 (Fig. 58)
- RICKETS**. A disease, marked by softening and deformation of the bones, due to deficiency of vitamin D. 93, 198, 225, 226 (Fig. 83)
- RUT**. Estrus; heat; the period in the sex cycle when a female animal will accept the male. 122
- SALIVA**. The moistening, lubricating, and starch-digesting secretion of the salivary glands. 155, 180, general 187-188, 248
- SALIVARY**, glands. Three sets of paired digestive glands which empty into the mouth. 32, 187
 secretion, 188-190
- SALT**. A readily ionizing substance formed when acid and alkali neutralize each other. regulation, 93-96
 see also Calcium; Potassium; Sodium
- SCAR**. The end result of healing of destroyed tissue. A tough, usually shrunken, wall of connective tissue.
 formation, 117
- SCURVY**. A disease, due to lack of vitamin C, marked by painful bleeding of the gums and joints. 198
- SECRETIN**. A hormone, liberated from the duodenum by acid, which stimulates secretion of pancreatic juice. general 83-85, 191, 193
- SECRETION**, 31-33, 83, 84, 178, 187, 188, 190, 191, 193, 248, 249
 by the kidney, 201
 of insulin, 99-100
 see Gastric; Hormones; Salivation
- SECRETOGOGUE**. A chemical agent which, circulating in the blood, stimulates secretion of certain glands, as of the stomach. 191
- SEGMENTAL NERVOUS SYSTEM**. The brain stem; the neuraxis. The segmental nervous system has repeated similar spinal nerves and other structures. 233 (Fig. 84), 234, 239
 see also Brain stem; Medulla; Midbrain; Neuraxis; Thalamus
- SEMINAL VESICLE**. A sac which contributes to the formation of semen and activates spermatazoa. 218 (Fig. 79), 219
- SEMI-PERMEABLE MEMBRANE**. A membrane which allows water and some dissolved substances to pass through but is impermeable to others. 53, 262
- SENSATION**. A conscious experience associated with afferent impulses normally set up by the stimulation of a receptor. 50, 51, general 67-71
 properties of, 62-67
 receptors for, 67-70
 see also Exteroceptive; Interoceptive; Proprioceptive
- SENSE ORGAN**, 36, 42, 49, 54, 60, 156
 role of, 61
 see also Exteroceptor; interoceptor
- SENSES**, general, 67-71
- SENSORY**. *See* Afferent
- SEPTICEMIA**. The presence of disease-producing bacteria in the blood stream. "Blood poisoning." 210
- SERUM**. The fluid which squeezes out from clotted blood. Compare plasma. 113, 114, 214, 215, 215 (Fig. 78), 216, 217

- SHAM RAGE. The behavior of a thalamic animal which simulates intense rage. 254
- SHIVERING, 104
- SHOCK. A state of prolonged low blood pressure following injury. Also a brief pulse of electric current serving as a stimulus. 110, 151
- SINUSOID. Capillary vessel, of such organs as liver and spleen, which is greatly widened and lined by actively phagocytic cells. 130, 172 (Fig. 64), 211 (Fig. 76)
- SKELETAL MUSCLE. Striated muscle; voluntary muscle; the main bulk of muscle, attached at each end to some bone. 3, 3 (Fig. 2), 4 (Fig. 3a)
see Muscle
- SKIN. *See* Epidermis
- SLEEP, 252
- SMOOTH MUSCLE. The non-striated, slowly acting muscle of the viscera. 27, 27 (Fig. 13), 28 (Fig. 14), 29 (Fig. 15)
see Muscle
- SNEEZE, 157
- SODIUM CHLORIDE. Common table salt. 107, 259, 260
regulation, 95-96
- SOFT PALATE. The fold of muscle and mucosa which separates the back portions of the cavities of the nose and the mouth. 155 (Fig. 56)
- SOL. The liquid, freely flowing state of a colloid. Compare Gel. 113, 261
- SPASMOPHILIA. Twitchings and overirritability, mainly in babies, resulting from a lowered amount of calcium in the blood. 94
- SPASTICITY. A state of excessive maintained muscular tension, often with some paralysis, due to lesions of the nervous system. 246
- SPECIFIC DYNAMIC ACTION. The ability of protein foods, especially, to evoke an increase in metabolism greater than that due to their own metabolism. 196
- SPECIFIC SYNTHESIS. The manufacture of particular appropriate substances which underlies growth and repair. 203
see also Defense; Growth; Reproduction
- SPERMATOGENESIS. The process of sperm formation in the testes. 218
- SPERMATOZOAN. Sperm; the male gamete or reproductive cell. 121, 218, general 218-219
- SPHINCTER. A circular band of extra-powerful muscle, able to prevent material in a hollow viscus from passing. 83, 193, 195
anal, 184
see also Pyloric
- SPINAL ANIMAL. An animal with the spinal cord cut across so that the lower cord functions by itself. 245, 246
- SPINAL CORD. The main length of the neuraxis, lying in the backbone. 38, 74, 76 (Fig. 32), 104, 233 (Fig. 84), 233, 235, 245, 246
- SPIROCHETE. A corkscrew-shaped protozoan; one type causes syphilis. 237
- SPLEEN. A viscus to the left of the stomach which, in part, stores red blood cells in concentrated masses. 119, 172
- STAPHYLOCOCCUS. A type of spherical bacterium which often causes infection, with much pus formation. 214
- STARCH, 187, 188, 190
- STEAP SIN. The fat-digesting enzyme of pancreatic juice. 192
- STETHOSCOPE. An instrument which aids the hearing of heart and other sounds. 142
- STIMULATION, 3 (Fig. 2), 10 (Fig. 7), 44 (Fig. 23), 47, 49-51, 56, 59, 60, 69, 71, 84, 193, 237

- STIMULUS.** A change in the environment which, if strong enough, will evoke a response. 9, 10 (Fig. 7), 15-17, 19, 47-49, 53, 54, general 58-61, 62, 63, 64 (Fig. 29), 65, 65 (Fig. 30), 70, 118, 188, 191, 204, 207, 246, 248
- STOMACH.** 156, 178-179 (Fig. 66), 180, 181 (Fig. 67), 183 (Fig. 68), 187, 191 (Fig. 70), 204, 229
contractions cf. 181-185, 186
see also Gastric
- STREPTOCOCCUS.** A type of spherical bacterium which often leads to "blood poisoning." 217
- STRIATED MUSCLE.** *See* Skeletal muscle. 3, 4 (Fig. 3a), 29, 30 (Fig. 16)
see Muscle.
- SUBTHRESHOLD.** Of intensity below that needed to stimulate. 59, 60
- SUGAR,** 118, 187, 188, 195, 196, 197, 200, 228, 262
regulation, 100 (Fig. 36)
synthesis, 22-23
see also Glucose; Glycogen
- SULPHANILAMIDE.** A new chemotherapeutic drug, especially effective against streptococcus infections. 217
- SULPHIAPYRIDINE.** Related to sulphanilamide but most effective in treating pneumonia. 217
- SUMMATION OF CONTRACTIONS.** The increased height of muscle response when a second contraction is initiated while the first is still in progress. 16
- SUMMATION OF STIMULI.** The cumulative action of rapidly repeated stimuli which renders two or more effective in producing a response although a single one is ineffective. 60
- SUPRASEGMENTAL NERVOUS SYSTEM.** The cerebrum and cerebellum and certain of their connections, added late in animal evolution and not repeated as is partly the segmental one. 233 (Fig. 84), 239
see also Cerebral cortex; Cerebrum; Cerebellum
- SWALLOWING,** 155-157, 180
- SWEAT GLAND,** 106
see also Perspiration
- SYMPATHETIC NERVOUS SYSTEM.** Used both for the autonomic nervous system as a whole or for its orthosympathetic portion. 76 (Fig. 32)
see Autonomic; Orthosympathetic; Parasympathetic
- SYMPATHIN.** A neurohumor liberated at orthosympathetic effectors when their nerves are active. 75, 118
- SYNAPSE.** The region of junction of two neurones or their processes. 41, 41 (Fig. 22)
- SYNCYTIUM.** A "supercell," with several nuclei, formed by the joining of smaller cells and loss of some cell walls.
see Cell, super
- SYNTHESIS,** 33, 197, 221
sugar, 22-23
- SYSTOLE.** The contraction phase of the heart beat. 30, 109, general 138-143
- TAMBOUR.** A shallow cylinder covered by a rubber membrane used to measure pressure changes. 164 (Fig. 61)
- TISTES.** Testicles; the male gonads or reproductive, sperm-forming organs. 85, 87, 128, 218, 218 (Fig. 79) 219
- TETANUS.** 1. The disease lock-jaw, characterized by muscle spasms. 2. A muscle contraction kept up by repeated stimuli at brief intervals. 17, 17 (Fig. 11), 18, 66, 94

- TETANY.** The symptom of general rigor and convulsions, most strikingly caused by deficient parathyroid hormone. 94
- THALAMUS.** The "bed" on which the cerebrum lies; the upper end of the brain stem. 223 (Fig. 84), 224, general 253-257
- THIRST,** 91, 92, 112
- THRESHOLD.** That intensity of a stimulus which just suffices to evoke a response. 67
- THROMBIN.** An enzyme-like substance, which clots fibrinogen, formed from a precursor in the blood. 114
formation of, 114-117
- THROMBOKINASE.** An activator which frees thrombin from its precursor during blood coagulation. 115, 116
- THROMBUS.** An intravascular blood clot. 114, 131, 132, 132 (Fig. 43)
- THYMUS.** An endocrine gland lying under the breast bone, most active in infancy. 85, 224
- THYROID.** An endocrine gland, placed as a "shield" on the windpipe below the voice box, the secretion of which increases cell metabolism. 85, 86 (Fig. 35), 87, 94, 104, 128, 227, 228
- THYROID-STIMULATING HORMONE.** One of the pituitary hormones. 87
- THYROXIN.** The active part of the hormone of the thyroid gland. 85, 228
- TIDAL AIR.** The amount of air (500 cc.) breathed in and out during a normal respiration. 163, 166
- TONSIL,** 213
- TOXIN.** A specific poisonous protein produced by certain kinds of bacteria. 208, 216
- TRACHEA.** The windpipe. 154, 154 (Fig. 55), 155, 157
- TRANSMISSION.** Conduction; propagation, the traveling of an impulse. 47, 73
see also Nerve impulse
- TRANSMITTER.** The mechanism—electric current or neurohumor—for transmitting an excitation across a junctional region. 57
- TRYPSIN.** The protein-digesting enzyme of the pancreas. 189, 192
- TRYPSINOGEN.** The inactive precursor of trypsin which is actually present in pancreatic juice. 192
- TUBERCLE.** A small hard mass of connective tissue; specifically such a mass formed about tubercle bacilli in tuberculosis. 210
- TUBERCULOSIS,** 160, 160 (Fig. 59), 210
- TUBULE.** A small tube-like arrangement of cells in some glands. 33, 198, 199, 199 (Fig. 71), 200, 219
- TWITCH.** A single muscle contraction. 9, 16, 16 (Fig. 10), 17 (Fig. 11), 28, 43, 44 (Fig. 23)
- TYPHOID.** A disease caused by the typhoid bacillus, marked by intestinal disturbances and high prolonged fever. 214, 215, 216, 217
- UMBILICAL CORD.** The "cord," containing blood vessels, connecting the fetus to the placenta. 219, 220 (Fig. 80)
- UNCONDITIONED REFLEX.** An inborn, unlearned reflex. 248
- UREA.** The main nitrogen-containing waste product of the catabolism of nitrogenous substances, as protein; secreted by the kidney tubules. 32, 101, 196, 200, 201
- URETER.** The duct carrying urine from each kidney to the urinary bladder. 199, 199 (Fig. 71), 204
- URETHRA.** The single duct which discharges urine, from the bladder, from the body. 218 (Fig. 79), 219
- URINARY BLADDER.** A sac of smooth muscle and mucous membrane which stores urine until urination. 199

- URINE. The watery solution of soluble waste products secreted by the kidney. 91, 173, 196, 200, 201
- UTERUS. The womb; the pear-shaped organ of smooth muscle and mucosa in which the embryo develops. 121, 123, 124 (Fig. 41), 125, 126, 204, 219
- VACCINATION. The process of introducing vaccine (weakened or killed bacteria or virus) into the skin to induce active immunity to a disease. 217
- VAGINA. The female genital passage, leading to the uterus. 120, 121 (Fig. 40), 124, 219
- VAGUS NERVE. Two main parasympathetic nerves, vagi, running from the medulla to nearly all the viscera. 55-57, 77, 99, 110, 111, 145, 157, 165, 165 (Fig. 62), 180, 189, 255
- VALVES, 133, 133 (Fig. 44), 137, general 138-142
disturbances of, 142-144
see also Aortic valves; A.V.; Ventriculo-arterial
- VARICOSE VEINS. Distended veins, usually in the legs, which may cause dropsy. 136
- VASCULAR. Referring to the blood vessels.
system, 111, 119, general 129-138, 148
- VASOCONSTRICTOR. An efferent nerve which constricts blood vessels, especially arterioles. 110, 111, 152
- VASODILATOR. An efferent nerve which dilates blood vessels, mainly arterioles. 110, 111
- VASOMOTOR. A collective term for vasodilator and vasoconstrictor nerves. 110, 111
- VEINS. The large-caliber, thin-walled vessels which carry blood towards the heart. 107, 109, 130, 131, 131 (Fig. 42), general 135-137, 138, 139, 148, 151
milking action on, 135 (Fig. 46), 136
see also Portal; Varicose
- VENA CAVAS. The two main veins, from the head and arms (superior vena cava) and from the trunk and legs (inferior vena cava). 107, 108 (Fig. 37), 139
- VENTRAL. On or towards the abdominal or belly side of the trunk; antonym of dorsal. 40
- VENTRICLE. The thick-walled chamber of each side of the heart which forces blood into the arteries. 108 (Fig. 37), 131, 133 (Fig. 44), 139, 140, 142, 144, 145, 146, 146 (Fig. 51)
- VENTRICULO-ARTERIAL VALVES. The valves, on each side of the heart, between ventricle and artery. The right is called the pulmonary semilunar; the left, the aortic semilunar. 40, 133 (Fig. 44)
- VILLI. The microscopic club-like protuberances which cover the surface of the mucosa of the small intestine. 177, 179 (Fig. 66)
- VIRUS. An infective agent which reproduces itself and produces disease while so growing in the tissues of a plant or animal. A virus causes smallpox, for example. 217
- VISCERA. The internal soft organs; sometimes limited to the contents of the chest and abdominal cavities. Singular, viscus. 68, 75, 76 (Fig. 32), 77, 78, 90, 110, 159, 204, 206 (Fig. 73), 227
visceral nervous system; *see* Autonomic
visceral sensation, 68-70, 71, 78, 206 (Fig. 73)
- VITAMIN, 93, 116, 117, general 198
- VOMITING, 186, 204
center, 186



WATER—absorption, 184, 200, 201

balance. The comparison between the amounts of water entering the body in drink (or formed from food) and leaving it in urine, sweat, exhaled air, etc. 195, 197, 198

chemistry of, 259-261

evaporation of, 106, 153

regulation, 90-93

WHITE CELL. White blood cell; leukocyte. 115, 117, 172, 208 (Fig. 74), 209 (Fig. 75), 214

see also Microphage

WHITE MATTER. The nerve fiber masses or tracts of the central nervous system, which appear white on section. 39 (Fig. 20), 40 (Fig. 21), 239

WINDPIPE. *See* Trachea

ZYGOTE. The product of union of egg and sperm; the first cell of a new individual. 218, 219, 224

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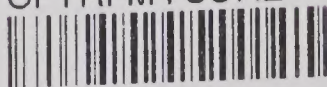
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